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The American Journal of CARDIOLOGY®

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Return to a natural rhythm

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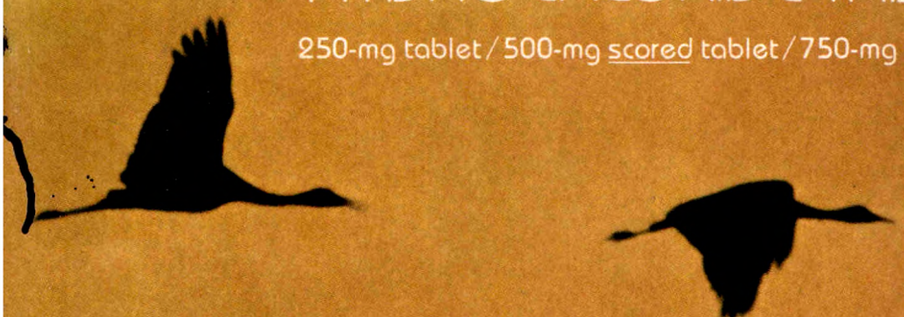

Enhances the value of oral procainamide for selected cardiac dysrhythmias

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Procan SR... the original sustained-release oral procainamide

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Please see next page for brief summary of prescribing information.

Procan® SR
(procainamide hydrochloride tablets)
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Before prescribing, please see full prescribing information.
A Brief Summary follows.

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: General —During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome.

Laboratory Tests—Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

Routine blood counts are advisable during maintenance procainamide therapy.

ADVERSE REACTIONS: Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS).

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride) tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dose of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dose of 0.5 to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED: Procan SR 250 mg (green, film-coated tablet. P-D 202) is available in bottles of 100 (N 0071-0202-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0202-40). Each sustained-release tablet contains 250 mg procainamide hydrochloride.

Procan SR 500 mg (yellow, scored, film-coated tablet. P-D 204) is available in bottles of 100 (N 0071-0204-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0204-40). Each sustained-release tablet contains 500 mg procainamide hydrochloride.

Procan SR 750 mg (orange, scored, film-coated tablet. P-D 205) is available in bottles of 100 (N 0071-0205-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0205-40). Each sustained-release tablet contains 750 mg procainamide hydrochloride.

Storage—Protect from moisture. Store bottles below 86° F (30° C). Store unit-dose packages at controlled room temperature, 59°-86° F (15°-30° C).

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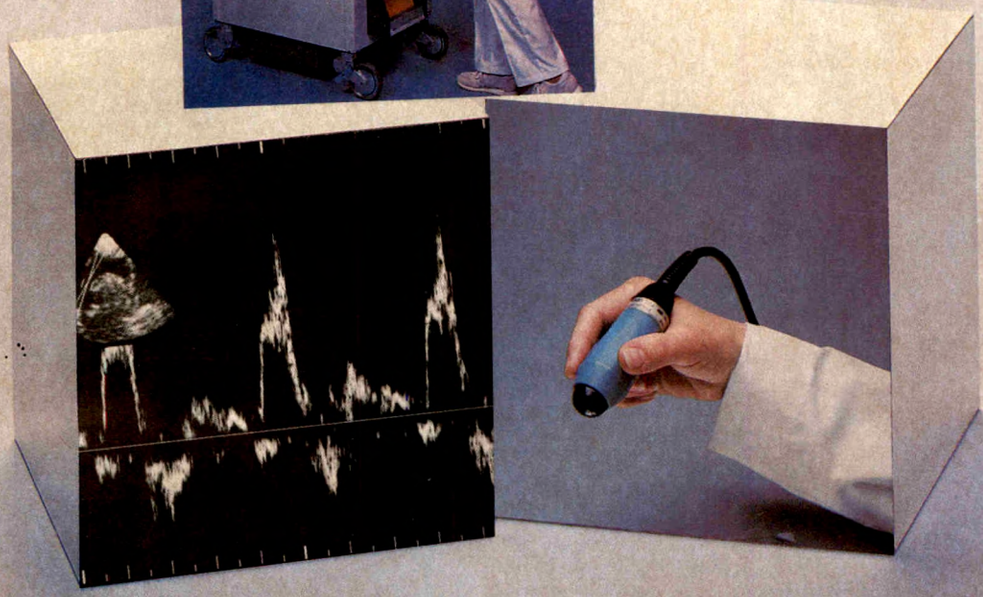

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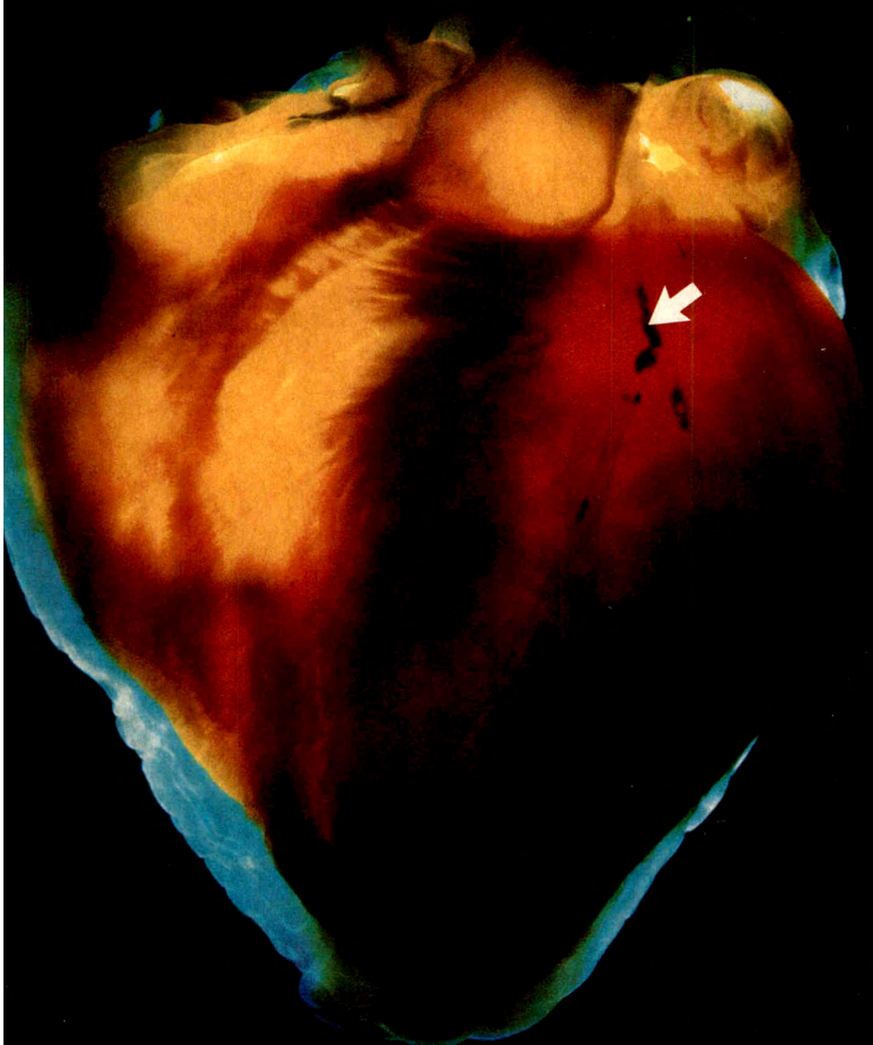

Calcified atherosclerotic plaques (arrow) are visible in branches of the left anterior descending artery (LAD) in this infrared photograph of a transilluminated cleared human heart. The epicardial fat appears blue or green, the atria and right ventricular wall appear yellow and the left ventricular myocardium is seen as red.

This extraordinary photographic technique enables investigators to study atherosclerotic plaque without opening or dissecting the vessels.

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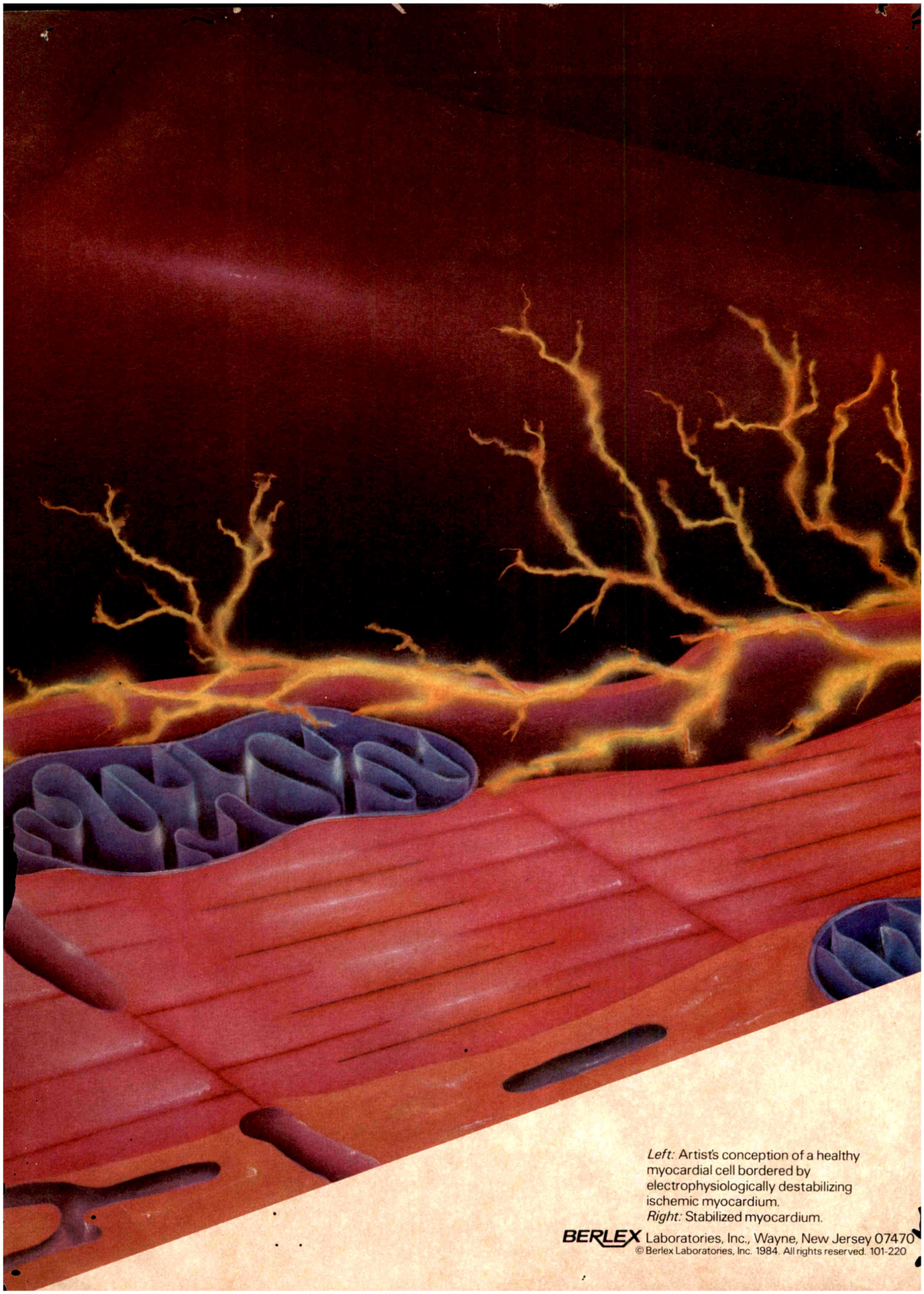

Left: Artist's conception of a healthy myocardial cell bordered by electrophysiologically destabilizing ischemic myocardium.
Right: Stabilized myocardium.

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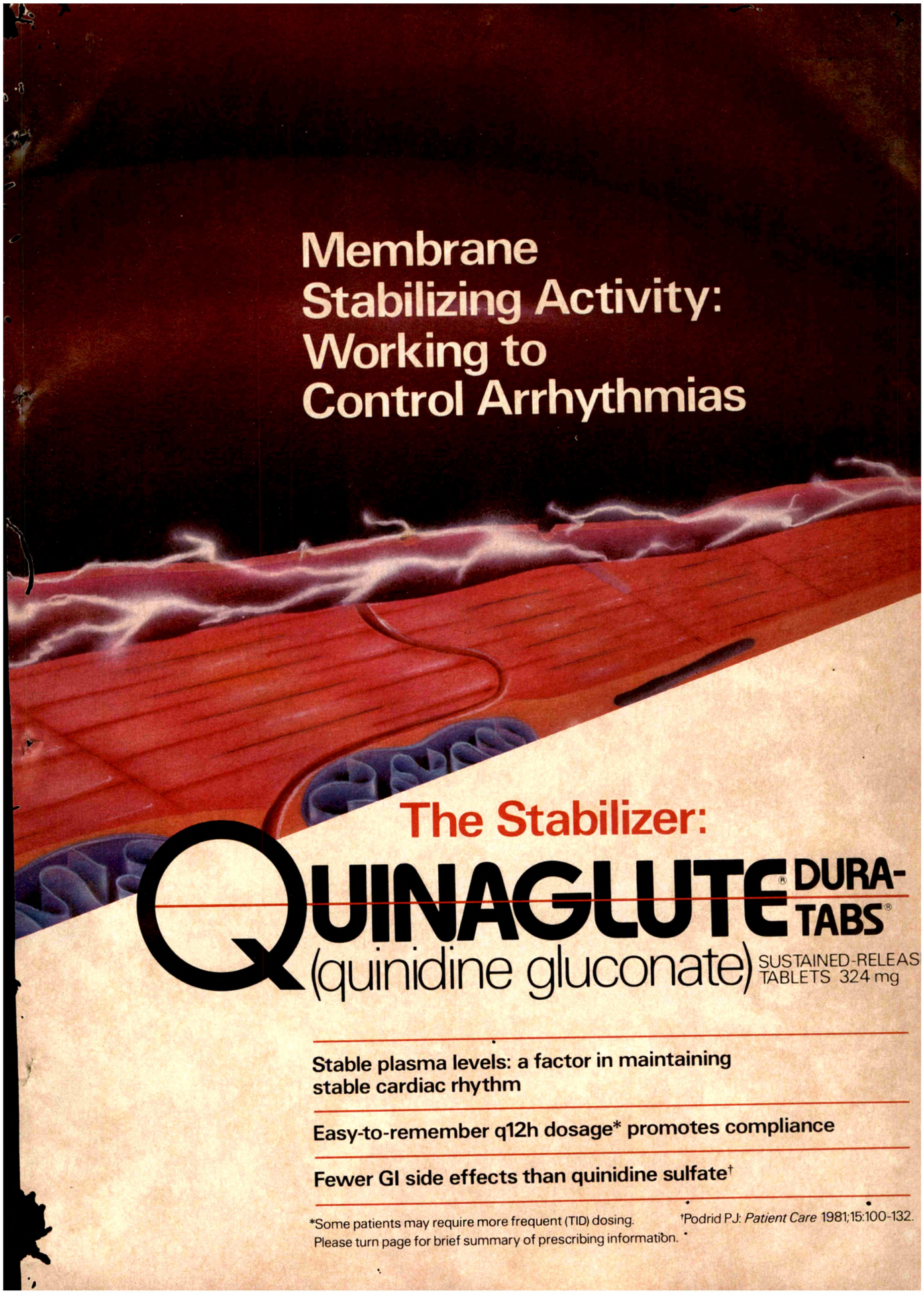

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†Podrid P.J: *Patient Care* 1981;15:100-132.

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INDICATIONS AND USAGE: Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:
1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).
2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).
CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.
2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.
3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.
4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.
5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.
7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.
8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.
Information for Patients: As with all solid oral medications, Quinaglute (quinidine gluconate) Dura-Tabs (sustained-release tablets) should be taken with an adequate amount of fluid, preferably in an upright position, to facilitate swallowing.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.
Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
See package insert for full information.
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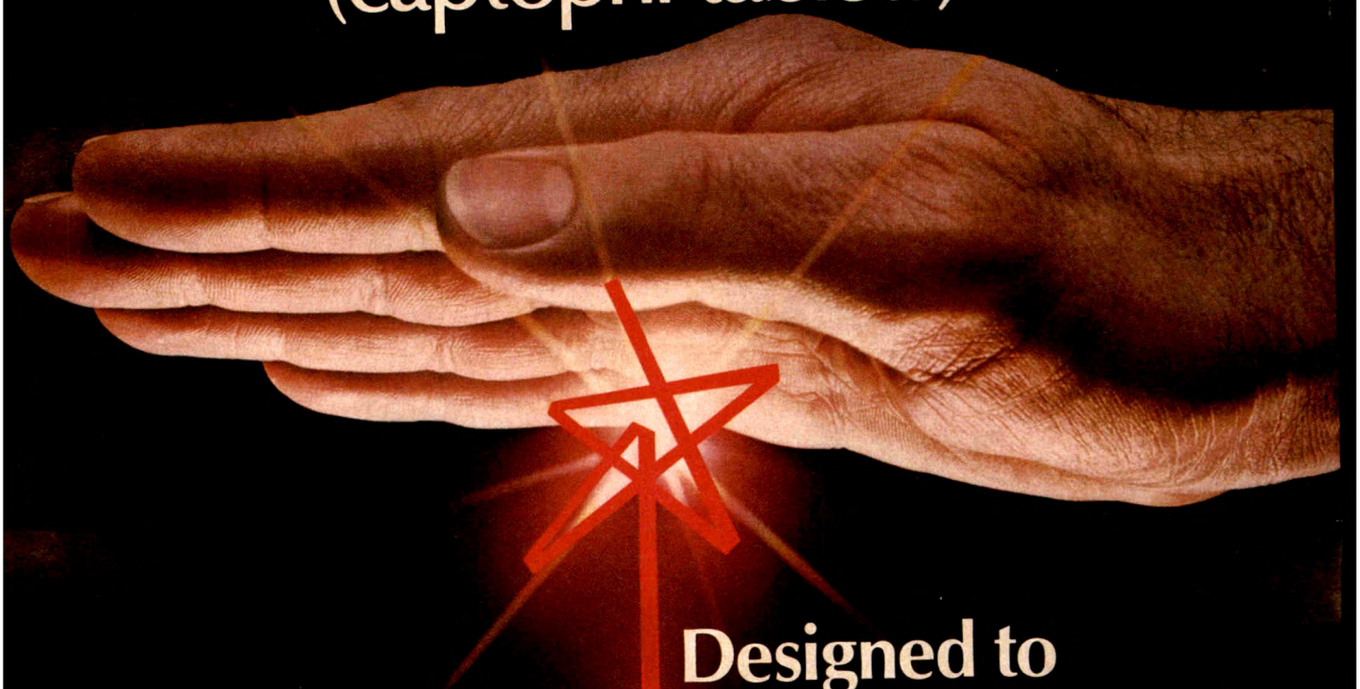

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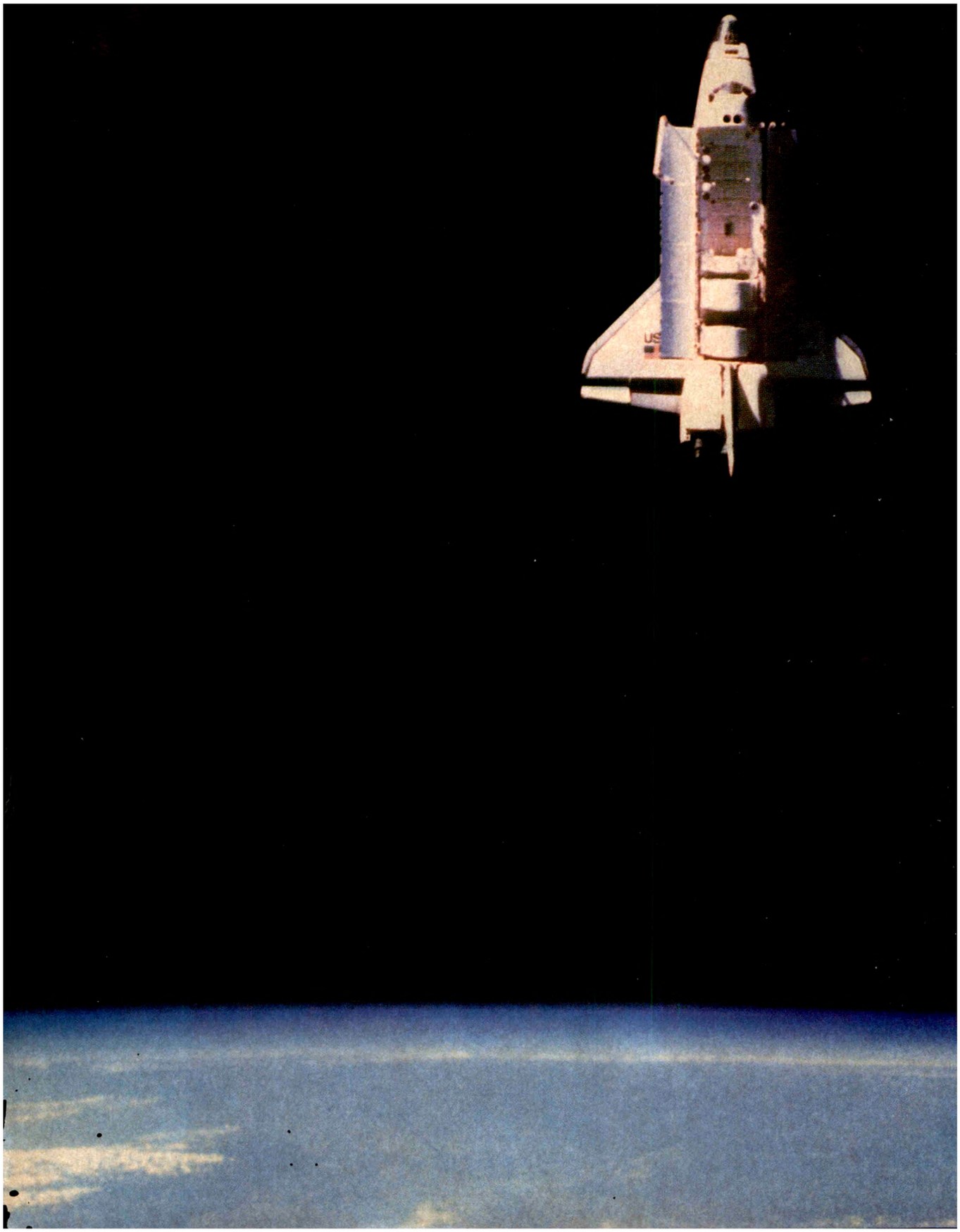

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5-mg and 10-mg Tablets

(pindolol)

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE
Visken® (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/ kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

	Total (Volunteered and Elicited)		
Body System/ Adverse Reaction	Visken (pindolol) (N = 322) %	Active controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

* Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

More than 7 million patient-years of experience

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and non-thrombocytopenic purpura.

Gastrointenstinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 5 mg b.i.d. alone or in combination with other antihypertensive agents. An antihypertensive response usually occurs within the first week of treatment. Maximal response, however, may take as long as or occasionally longer than two weeks. If a satisfactory reduction in blood pressure does not occur within 3-4 weeks, the dose may be adjusted in increments of 10 mg per day at these intervals up to a maximum of 60 mg per day.

HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05).

[VIS-Z3 6/15/83]

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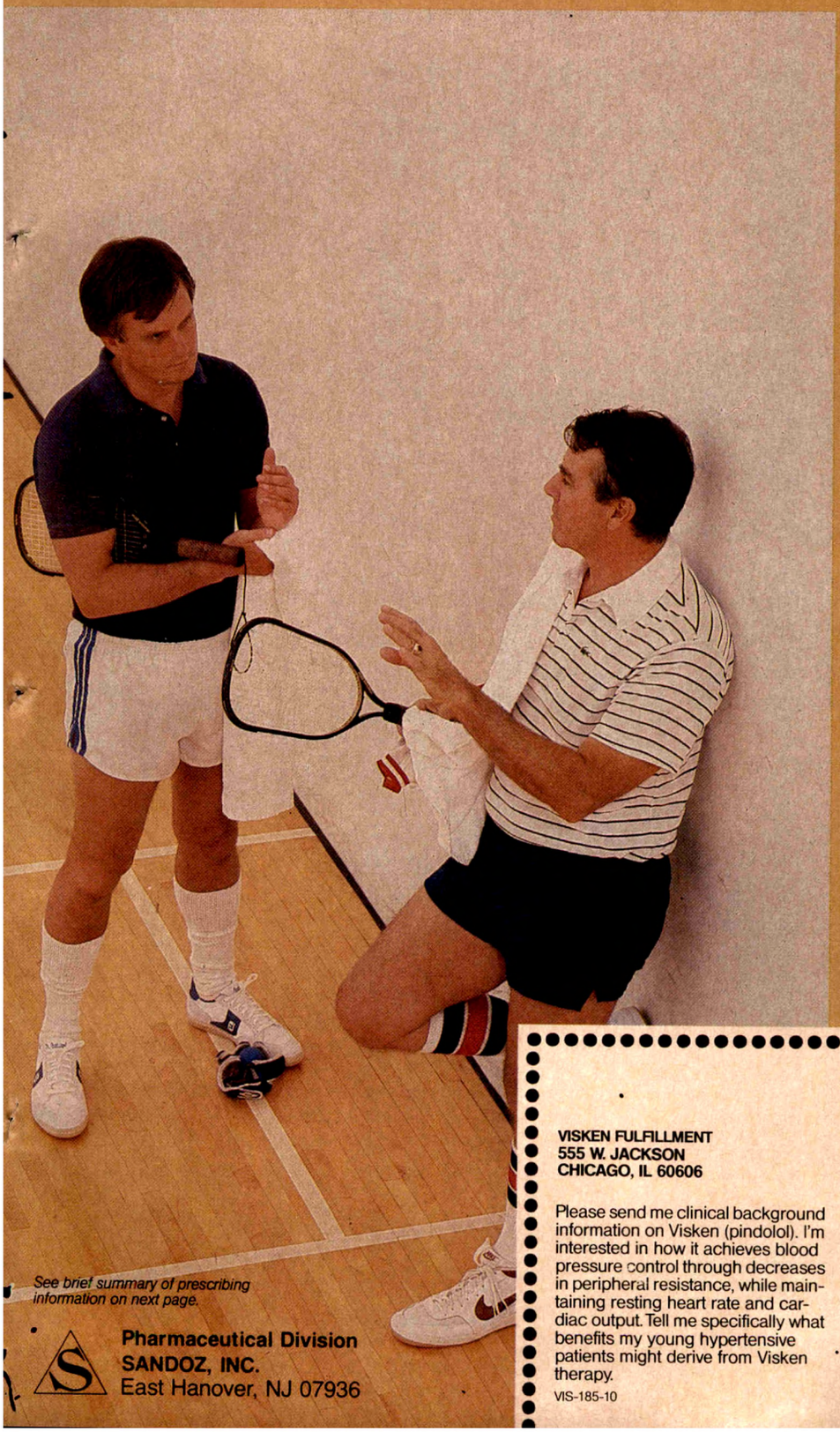

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See brief summary of prescribing information on next page.

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City_____ State_____ ZIP_____

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VOLUME 55

NUMBER 1

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CORONARY HEART DISEASE

1 **Baseline Rest Electrocardiographic Abnormalities, Antihypertensive Treatment, and Mortality in the Multiple Risk Factor Intervention Trial**

MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP

This report presents further analyses pertaining to a previously reported adverse mortality trend in a subgroup of participants in the Multiple Risk Factor Intervention Trial. The adjusted coronary artery disease (CAD) mortality rate was 67% higher in hypertensive men in the special-intervention (SI) group with baseline electrocardiographic abnormalities at rest than in corresponding men in the usual-care (UC) group. Abnormalities were primarily R- or ST-T-wave changes. The higher CAD mortality rate in the SI group was manifested chiefly as sudden death within 1 hour. Men in the SI group with electrocardiographic abnormalities at rest who had been given diuretic drugs (hydrochlorothiazide or chlorthalidone) had a 3-fold higher CAD mortality rate than those not given diuretic drugs. This increased relative risk (diuretics/no diuretics) was not seen among SI men with a normal electrocardiogram at rest nor in the UC group. No relation with diuretic dose or hypokalemia was found.

16 **Exercise Electrocardiogram and Coronary Heart Disease Mortality in the Multiple Risk Factor Intervention Trial**

MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP

The Multiple Risk Factor Intervention Trial, a primary prevention trial, revealed a 7% lower coronary heart disease (CAD) mortality rate (nonsignificant) in the group randomized to special intervention (SI) to reduce blood cholesterol levels, diastolic blood pressure, and cigarette smoking, compared with a group assigned to usual care (UC). In the UC group the 12% of men with an abnormal ST depression integral in response to heart-rate-limited exercise had 3 times the rate of CAD death of those with a normal test response. Contrary to the result that had been predicted for the subgroup with a normal response, there was no SI-UC difference in CAD mortality. However, in the subgroup with an abnormal response, the CAD mortality rate was 57% lower in SI than UC participants.

26 **Relation of Antianginal Efficacy of Nifedipine to Degree of Coronary Arterial Narrowing and to Presence of Coronary Collateral Vessels**

WOLFGANG SCHULZ, STEFAN JOST, GISBERT KOBER, and MARTIN KALTENBACH

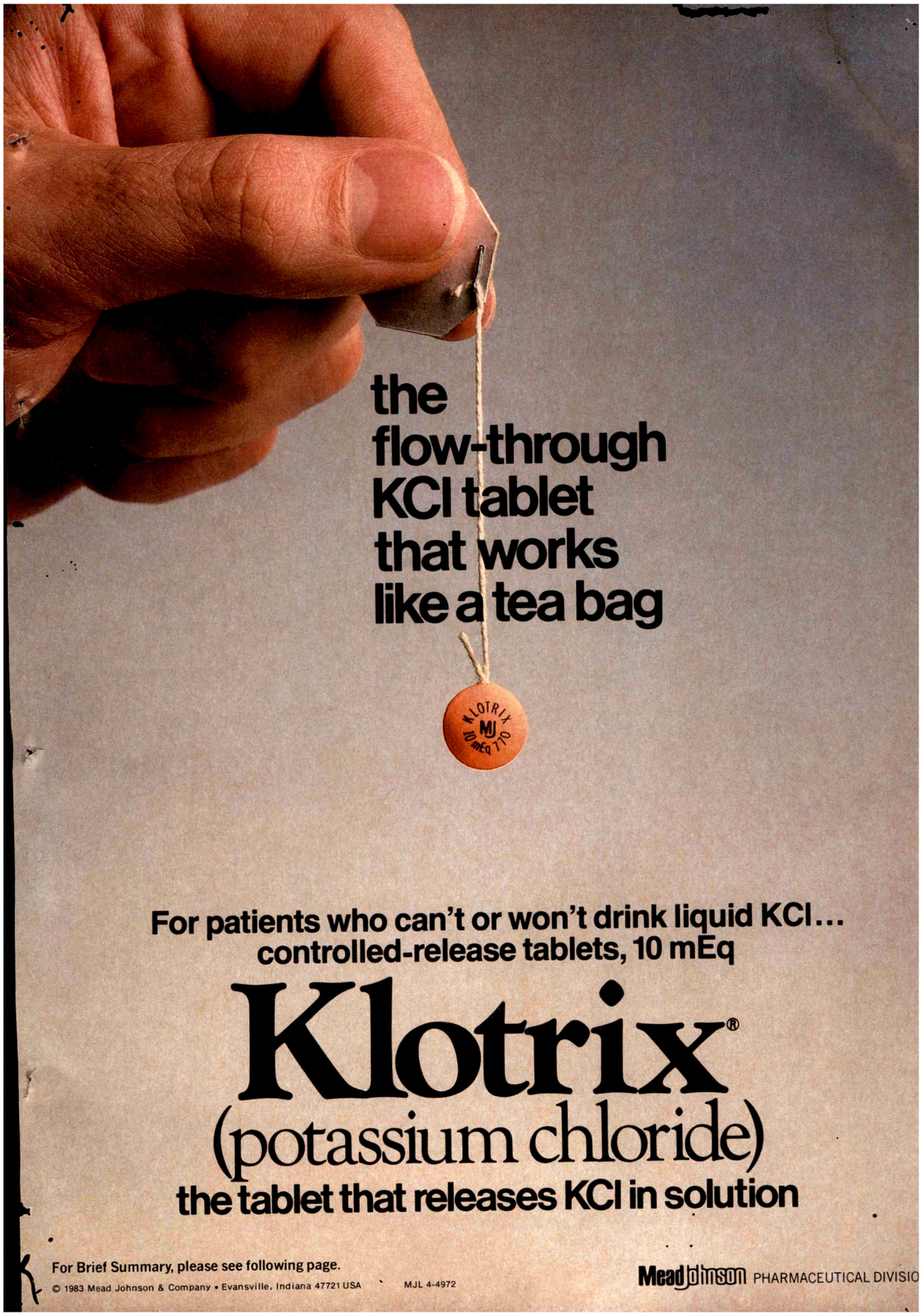
Patients who do not respond to nifedipine have been reported in many studies. A reflex tachycardia, cited as explanation, is often not present. To test if there is evidence for a "coronary steal" phenomenon in patients who do not respond to nifedipine treatment, 36 selected patients with coronary artery disease were separated into 2 groups: those in whom a coronary steal appeared possible (occlusions and collaterals, group B, C and D) and those in whom it was not possible (stenoses and no collaterals, group A). Patients underwent repetitive exercise tests after double-blinded crossover treatment with 20 mg of nifedipine, 20 mg of isosorbide dinitrate, the combination of both and placebo. After nifedipine, ST-segment depression and angina pectoris were reduced only in group A; after isosorbide dinitrate, ST-segment depression and angina pectoris were reduced in all groups. An inadequate increase in heart rate was not found among those who did not respond to nifedipine. It is concluded that steal-like mechanisms are responsible for the lack of response to nifedipine treatment.

33 **Coronary Hemodynamic and Metabolic Effects of Nifedipine in Patients with Coronary Artery Disease Treated with Beta-Blocking Drugs**

PETER SCHANZENBÄCHER, GERHARD GÖTTFERT, GERHART LIEBAU, and KURT KOCHSIEK

The coronary hemodynamic and metabolic effects of nifedipine were studied after propranolol-induced β-receptor blockade in 12 patients with coronary artery disease. Propranolol led to a decrease in heart rate, coronary blood flow and myocardial oxygen consumption and to an increase in coronary vascular resistance and the coronary arteriovenous oxygen difference. Subsequent administration of nifedipine resulted in a transient increase in coronary blood flow, a reduction in coronary vascular resistance and the coronary arteriovenous oxygen dif-

Continued on page A23



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DESCRIPTION KLOTRIX is a film-coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS—BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg,* spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with potassium-sparing diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg,* spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KLOTRIX is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. KLOTRIX should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

ADVERSE REACTIONS Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose. One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

Note: KLOTRIX® slow-release tablets must be swallowed whole and never crushed or chewed. Following release of the potassium chloride, the expended wax matrix, which is not absorbed, may be observed in the stool.

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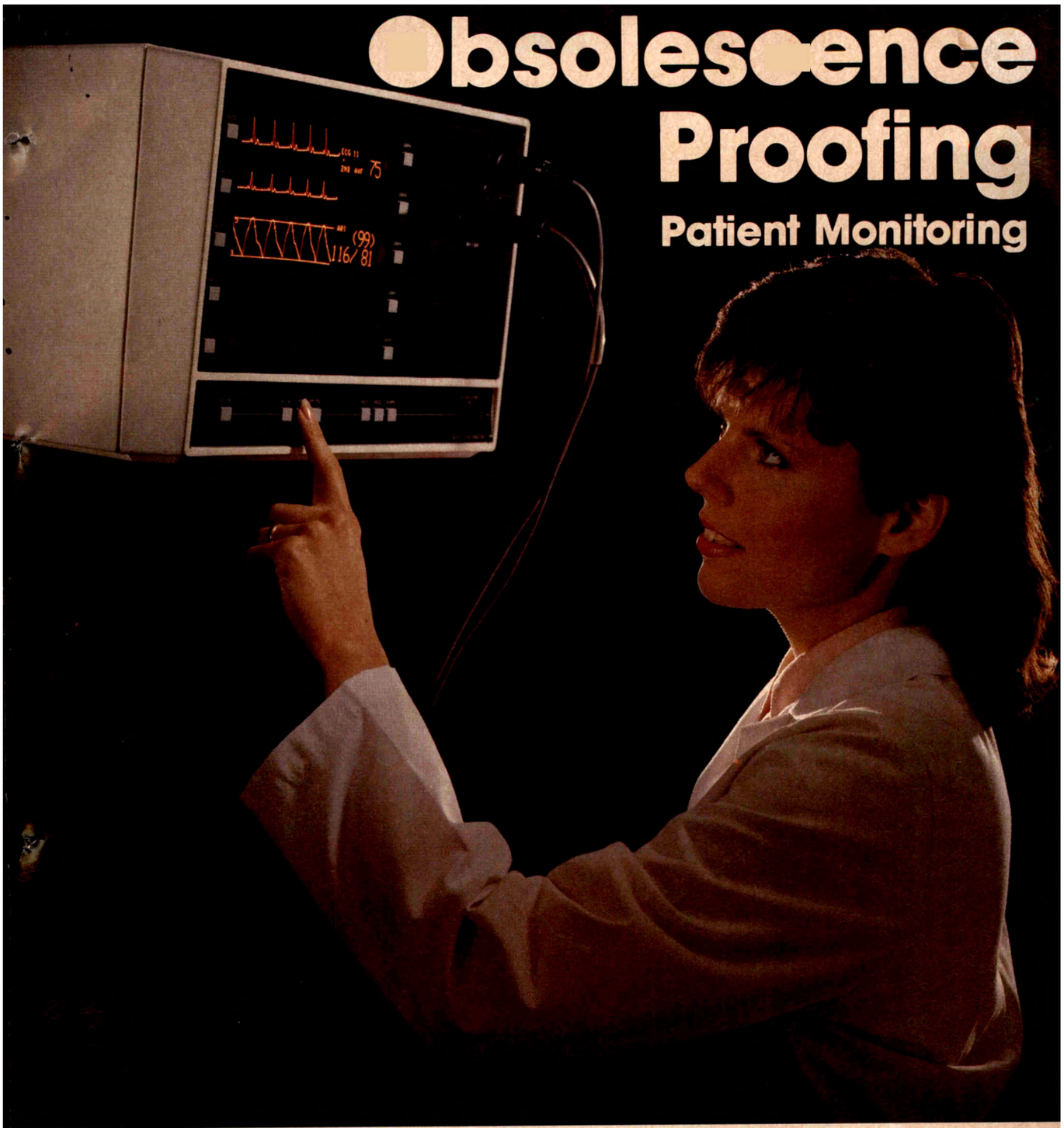

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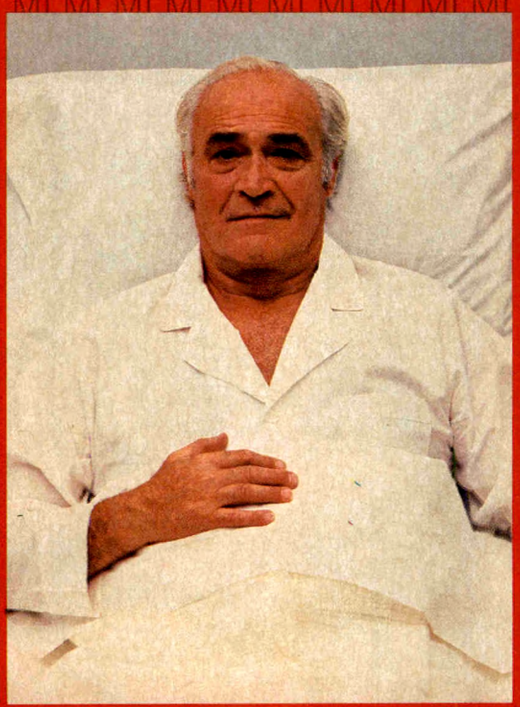

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1. The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. *304(14)*:801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see below); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

In patients with nonallergic bronchospasm or with a history of nonallergic bronchospasm (e.g., chronic bronchitis, emphysema), BLOCADREN should be administered with caution.

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BLOCADREN®
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CONTRAINDICATIONS:

BLOCADREN is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal – Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm: In patients with nonallergic bronchospasm or with a history of nonallergic bronchospasm (e.g., chronic bronchitis, emphysema), BLOCADREN should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol (see OVERDOSAGE).

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: Impaired Hepatic or Renal Function: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN® (Timolol Maleate, MSD) is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported. When using these agents concomitantly, patients should be observed carefully to confirm that the desired therapeutic effect has been obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy – Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
SKIN		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure – Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema – Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed. These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole:* extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive:* gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Hematologic:* nonthrombocytopenic purpura; *Endocrine:* hyperglycemia, hypoglycemia; *Skin:* rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* arthralgia; *Nervous System:* local weakness; *Psychiatric:* depression, nightmares, somnolence, insomnia, nervousness, diminished concentration, hallucinations; *Respiratory:* cough; *Special Senses:* visual disturbances, diplopia, ptosis, dry eyes; *Urogenital:* impotence, urination difficulties.

There have been reports of retroperitoneal fibrosis in patients receiving timolol maleate and in patients receiving other beta-adrenergic blocking agents. A causal relationship between this condition and therapy with beta-adrenergic blocking agents has not been established.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN® (Timolol Maleate, MSD), but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System:* reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular:* intensification of AV block (see CONTRAINDICATIONS); *Digestive:* mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* agranulocytosis, thrombocytopenic purpura; *Allergic:* erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous:* reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations. 183 (DC7117616)

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ference and a sustained decrease in mean aortic pressure and myocardial oxygen consumption. Thus, the ability of nifedipine to dilate the coronary vasculature was effective in reversing the inappropriate vasoconstriction caused by propranolol, while maintaining an oxygen saving effect for the heart.

37 Value of Arm Exercise Testing in Detecting Coronary Artery Disease

GARY J. BALADY, DONALD A. WEINER, CAROLYN H. McCABE, and THOMAS J. RYAN

To determine the sensitivity of arm exercise in detecting coronary artery disease, 30 patients with a history of angina and angiographically proved CAD (≥70% stenosis in 1 or more vessels) performed both arm ergometry and treadmill testing. Ischemic ST-segment depression (>1 mm) or angina occurred more frequently with leg exercise than with arm exercise (86% vs 40%, respectively $p < 0.001$), although there was no significant difference in peak rate-pressure product achieved with either test. Peak oxygen consumption was greater during leg exercise than during arm exercise (18 vs 13 ml/kg/min, $p < 0.001$). For the patients with concordantly positive tests, the oxygen consumption at the onset of ischemia was significantly lower during arm testing than during leg testing (12 vs 17 ml/kg/min, $p < 0.001$). There was no significant difference in heart rate during either test at the onset of ischemia. Thus, arm exercise testing is less sensitive than leg exercise in detecting CAD, but is a reasonable alternative in patients who cannot perform lower extremity exercise.

40 Coronary Risk Factors and Their Pathway of Action Through Coronary Raised Lesions, Coronary Stenoses and Coronary Death. Multivariate Statistical Analysis of an Autopsy Series: The Oslo Study

INGAR HOLME, LARS A. SOLBERG, LISA WEISSFELD, ANDERS HELGELAND, INGVAR HJERMANN, PAUL LEREN, JACK P. STRONG, and O. DALE WILLIAMS

From 1972 to 1980, results of 204 consecutive autopsy cases from the Oslo Study cohort of 16,202 40- to 49-year-old men were obtained from whom information of risk factors as serum cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic blood pressure, cigarette smoking, physical activity at work and at leisure, and social class was available. This report describes the strong relation found between coronary raised lesions, coronary stenoses, and death from coronary heart disease and risk factors such as serum cholesterol, high-density lipoprotein cholesterol and blood pressure. None of the other coronary risk factors appeared to be significantly related to stenosis when raised lesion was used as an independent variable.

48 Percutaneous Transluminal Coronary Angioplasty After Intracoronary Streptokinase in Evolving Acute Myocardial Infarction

SILVIO E. PAPAPIETRO, WILLIAM A. H. MacLEAN, ALFRED W. H. STANLEY, Jr., RANDALL G. HESS, NAN CORLEY, JOAQUIN G. ARCINIEGAS, and TERRY B. COOPER

Percutaneous transluminal coronary angioplasty (PTCA) was attempted in 18 patients with acute myocardial infarction after administration of intracoronary streptokinase. After thrombolytic therapy, 11 patients had a severe residual stenosis and 7 patients a persistent total occlusion of the infarct-related artery. PTCA was successful in 13 of 18 patients (72%): in 9 of 11 with stenoses and in 4 of 7 with total occlusions. PTCA reduced the severity of the coronary diameter narrowing from 91 ± 2% to 27 ± 7% ($p < 0.001$) and the transstenotic pressure gradient from 38 ± 5 to 6 ± 2 mm Hg ($p < 0.01$). One patient in shock died during urgent coronary surgery after unsuccessful PTCA. One patient had anterolateral reinfarction with reocclusion of the left anterior descending artery 5 days after PTCA. Twelve patients had an uneventful hospital course, and cardiac catheterization before hospital discharge (8 to 17 days) revealed reocclusion of the infarct-related coronary artery in 3 and persistent patency of the artery in 9. Persistent patency of the infarct-related artery was associated with preservation of left ventricular end-diastolic volume (initial 86 ± 6 ml/m^2; follow-up 91 ± 6 ml/m^2), and improvement in left ventricular ejection fraction in some patients.

54 Positive Exercise Thallium-201 Test Responses in Patients with Less Than 50% Maximal Coronary Stenosis: Angiographic and Clinical Predictors

KENNETH A. BROWN, MARY OSBAKKEN, CHARLES A. BOUCHER, H. WILLIAM STRAUSS, GERALD M. POHOST, and ROBERT D. OKADA

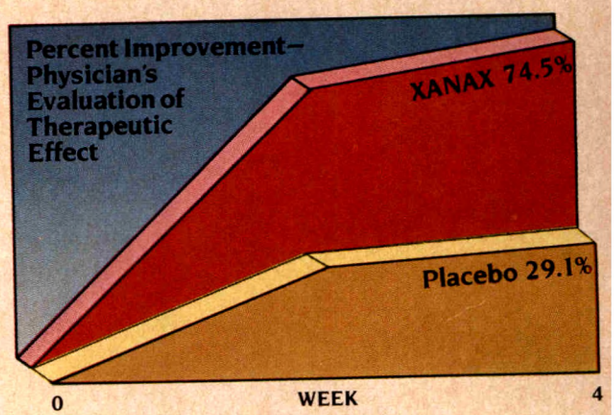
The incidence and causes of abnormal thallium-201 myocardial perfusion studies in patients with maximal angiographic coronary stenosis of less than 50% were examined in 100 patients. Maximal coronary stenosis ranged from 0 to 40%. Logistic regression analysis was performed using clinical, exercise and angiographic data. Significant predictors of a positive stress thallium-201 test were: percent maximal coronary stenosis ($p < 0.0005$), propranolol use ($p < 0.01$), interaction of propranolol use and percent maximal stenosis ($p < 0.01$), and stress-induced chest pain ($p = 0.05$). Positive thallium tests were more common in patients with maximal stenosis of 21 to 40% compared to maximal stenosis of 0 to 20% and were especially common in patients with 21 to 40% stenoses who reached 85% maximal predicted heart rate. Patients taking propranolol more frequently had positive thallium-201 tests than patients not taking propranolol. Individual perfusion defects corresponded well to the

Continued on page A27

Xanax rapidly relieves anxiety...

In double-blind, four-week, clinical trials in 976 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.[1]

XANAX was significantly more effective ($p<0.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).



...including cardiovascular symptoms of anxiety...

Most patients in the study had cardiovascular symptoms even though cardiovascular disease was ruled out. XANAX was shown to effectively relieve anxiety including the accompanying cardiovascular symptoms.

...and depressive symptoms of anxiety.

Over 70% of these patients experienced moderate to severe depressed mood. XANAX was shown to be significantly more effective ($p<0.014$) than placebo in improving depressed mood.

1. Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* 1981;42:347-351.

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XANAX® Tablets
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CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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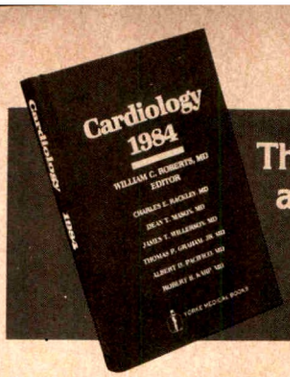

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presence of a 21 to 40% stenosis in the coronary artery that supplied that region. The high frequency of thallium-201 defects associated with 21 to 40% stenosis and an observed close correspondence of such defects with territory supplied by these stenoses suggests that such coronary lesions may have true hemodynamic impact. In addition, the high incidence of positive thallium-201 test results in patients taking propranolol suggests that an attempt be made to wean patients off β blockade before exercise thallium testing.

58 Collateral Circulation in Coronary Artery Disease

MacARTHUR A. ELAYDA, VIRENDRA S. MATHUR, ROBERT J. HALL, G. ALI MASSUMI, EFRAIN GARCIA, and CARLOS M. de CASTRO

Collateral circulation was assessed among patients with severe coronary artery disease. Two hundred two consecutive patients were studied. Of the 127 patients who had at least 1 major branch that was totally occluded, collateral circulation was seen angiographically in 125, whereas collateral circulation was seen in only 2 of the 75 patients without total occlusion; both had 99% (near-total) occlusion. Thus, collateral circulation cannot be seen angiographically unless there is total or near-total occlusion. Left ventricular wall motion analysis indicates that an akinetic area can exist despite good collateral flow and normal wall motion can be seen in area of occluded artery despite poor collateral flow to that segment.

61 Influence of Magnesium Ion on Human Ventricular Defibrillation After Aortocoronary Bypass Surgery

BERNICE R. HECKER, CAROL L. LAKE, IRVING L. KRON, ROBERT M. MENTZER, IVAN K. CROSBY, STANTON P. NOLAN, and RICHARD S. CRAMPTON

Although administration of magnesium ion (Mg^{++}) produces spontaneous ventricular defibrillation and decreases the incidence of arrhythmias in various clinical conditions, a beneficial effect of administration of Mg^{++} during cardiac surgery could not be demonstrated. Neither spontaneous ventricular defibrillation nor a decreased incidence of arrhythmias occurred. Administration of Mg^{++} before cardiopulmonary bypass increased the number of shocks and the level of energy required for direct ventricular defibrillation. Elevation of the concentration of plasma magnesium during cardiac surgery above 2.3 mg/dl, the midnormal range, cannot be recommended.

65 Remnant Saphenous Veins After Aortocoronary Bypass Grafting: Analysis of 3,394 Centimeters of Unused Vein from 402 Patients

BRUCE F. WALLER and WILLIAM C. ROBERTS

The status of saphenous veins intended for use as aortocoronary bypass grafts was determined from a histologic survey of 3,394 cm of unused veins excised from 402 patients who underwent bypass operations. Over 90% of 6,788 five-millimeter-long remnant segments had some degree of intimal fibrous thickening, including 16 (0.4%) segments from 10 patients that were narrowed 76 to 100% in cross-sectional area. Preexisting saphenous vein disease may account for some of the variability in intimal changes observed within the same bypass graft or among different grafts in the same patient.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

72 Chronic Lorcainide Therapy for Symptomatic Premature Ventricular Complexes: Efficacy, Pharmacokinetics and Evidence for Norlorcainide Antiarrhythmic Effect

R. HARDWIN MEAD, DEBORAH L. KEEFE, ROBERT E. KATES, and ROGER A. WINKLE

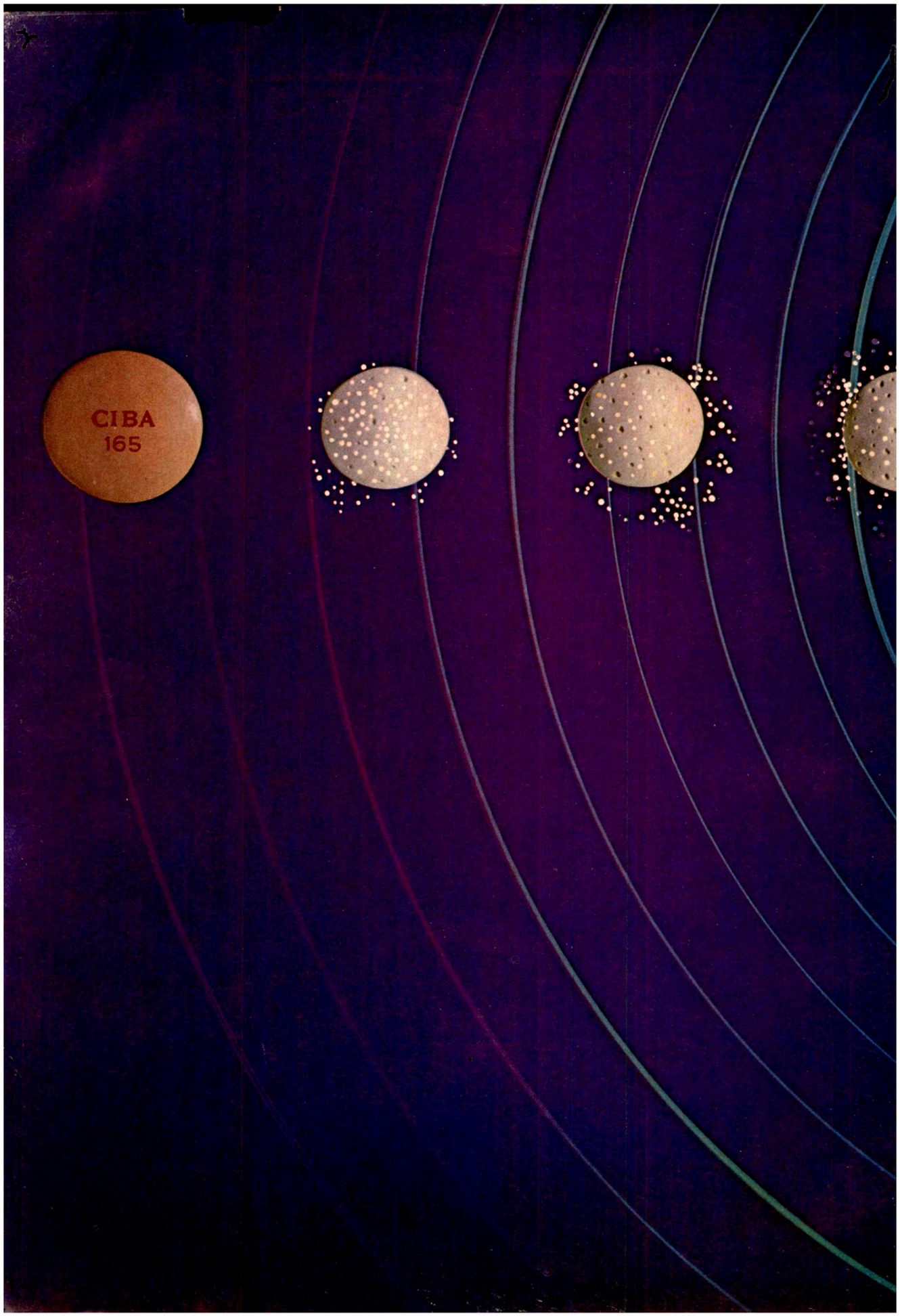
This study evaluates the long-term efficacy of lorcainide in suppressing chronic symptomatic ventricular premature beats, and examines the relation of arrhythmia suppression to plasma concentrations of lorcainide and norlorcainide, a metabolite that accumulates after repeated oral doses. Fourteen patients were treated with lorcainide, 200 to 400 mg/day; 12 achieved nearly complete suppression of arrhythmias within 1 year. Lorcainide and norlorcainide plasma concentrations remained stable after the first week of therapy. Antiarrhythmic activity persisted throughout the year. On drug withdrawal after 1 year, the norlorcainide washout half-life was more than twice that of lorcainide, and the return of arrhythmias occurred after the lorcainide plasma concentration had fallen to subtherapeutic levels, suggesting an antiarrhythmic effect of norlorcainide. Therapy was well tolerated in the majority of patients.

79 Flecainide: Long-Term Treatment Using a Reduced Dosing Schedule

DAVID FLOWERS, DEBORAH O'GALLAGHER, VILMA TORRES, DENNIS MIURA, and JOHN C. SOMBERG

Flecainide is a new antiarrhythmic agent that was initially prescribed at 200 mg twice daily, but after reports of early toxicity, the dose was reduced to 100 mg twice daily. The efficacy of flecainide at the reduced dosage regimen was studied in 40 patients. Programmed electrical stimulation induced sustained ventricular tachycardia in

Continued on page A32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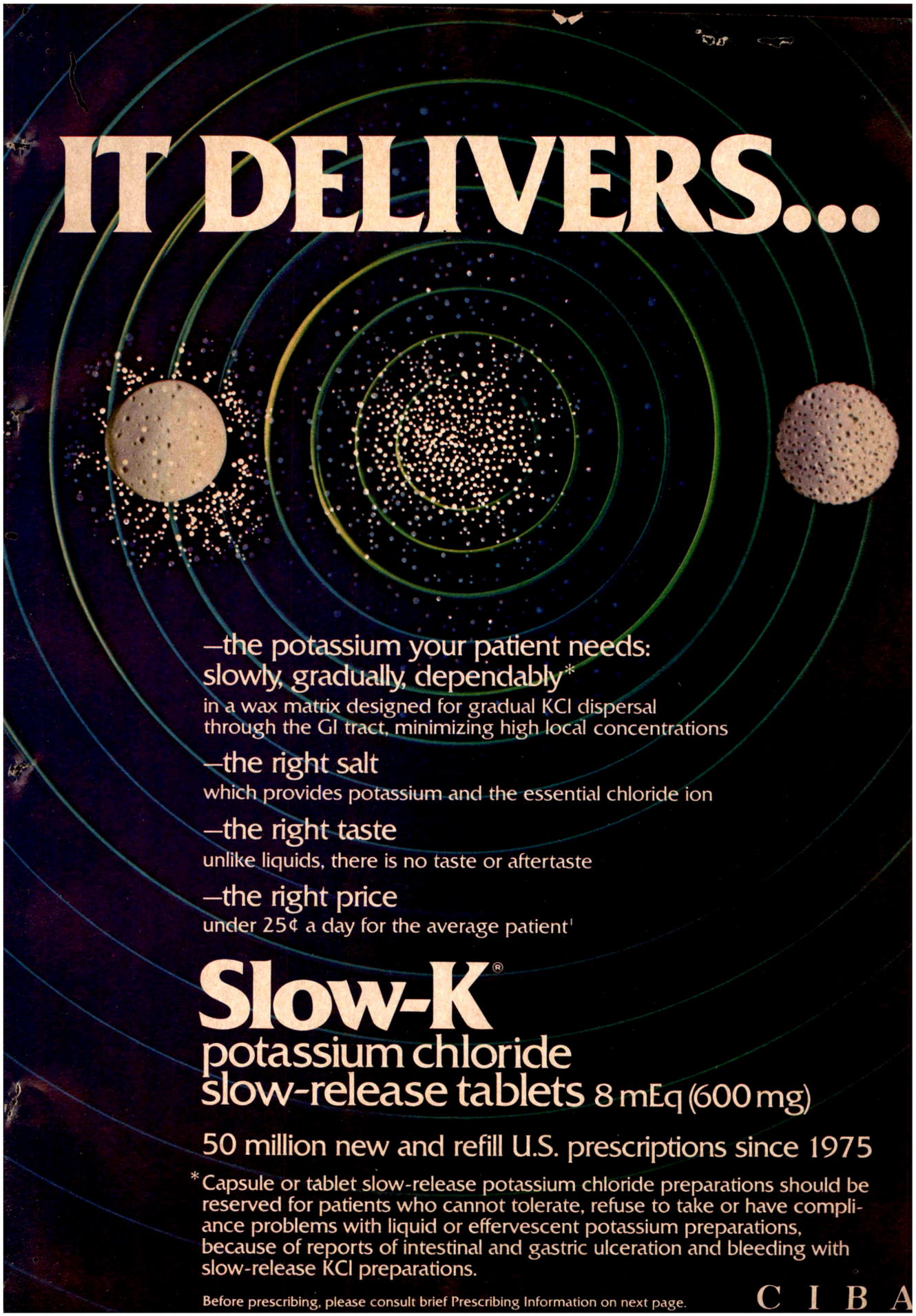
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Before prescribing, please consult brief Prescribing Information on next page.
CIBA

Reference
1. Data on file. CIBA Pharmaceutical Company

SLOW-K® potassium chloride **slow-release tablets**

Brief Summary of Prescribing Information

DESCRIPTION

Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure; systemic acidosis such as diabetic acidosis; acute dehydration; extensive tissue breakdown as in severe burns; adrenal insufficiency; or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalemia: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years),cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS

The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

ADVERSE REACTIONS

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications, Warnings and Overdosage). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION

The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C82-58 (Rev 1/83)

Consult complete product literature before prescribing.

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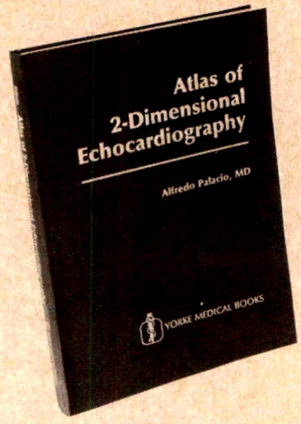

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Foreword by David H. Spodick, MD, DSc
Professor of Medicine, University of Massachusetts Medical School; Director, Division of Cardiology, St. Vincent Hospital, Worcester, Massachusetts

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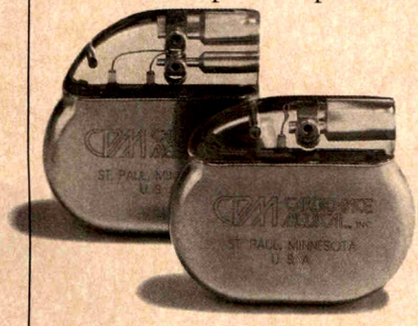

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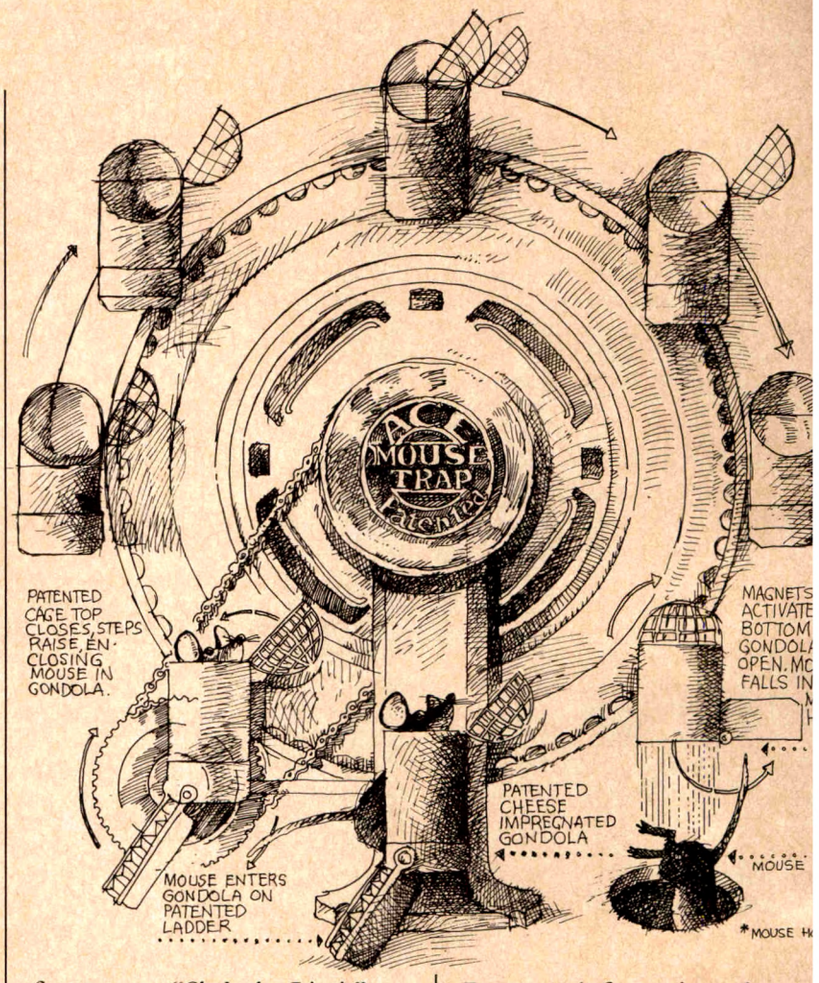

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21 patients and nonsustained ventricular tachycardia in 19. Flecainide prevented ventricular tachycardia induction in 26 patients (65%). Twenty-one patients were discharged on flecainide therapy, 100 mg twice daily, and were followed up a mean of 11 months; all ventricular tachycardia events were abolished, with an 85% reduction in ectopy. Sixteen patients are alive and well, 1 patient died suddenly, 1 died from noncardiac causes and 1 had a breakthrough arrhythmia. Thus, flecainide therapy guided by programmed electrical stimulation is effective at a reduced dose.

84 Effect of Electrical Activation Site on Left Ventricular Performance in Ventricular Tachycardia Patients with Coronary Heart Disease

JOEL S. RAICHLEN, JONATHAN M. LINKS, and PHILIP R. REID

The effect of alterations in the site of ventricular activation was examined by endocardial pacing in 10 patients with coronary disease who were undergoing evaluation for recurrent ventricular arrhythmias. During right ventricular (RV) pacing sequences, radionuclide ventriculograms were acquired for calculation of left ventricular (LV) volumes. When compared to pacing from the RV outflow tract, RV apical pacing resulted in higher end-diastolic volume ($p = 0.020$), end-systolic volume ($p = 0.041$), stroke volume ($p = 0.046$), peak rate of LV ejection ($p = 0.034$), and peak rate normalized for differences in end-diastolic volume ($p = 0.047$). These higher volumes and ejection rates for RV apical vs RV outflow tract pacing occurred with different radionuclide patterns of emptying and an increase in LV/RV stroke count ratio ($p = 0.030$), suggesting the development of mitral regurgitation. These differences suggest that the anatomic site of origin for ectopic foci may be an important determinant of the hemodynamic consequences of ventricular tachycardia.

89 Intravenous and Oral Loading Versus Oral Loading Alone with Amiodarone for Chronic Refractory Ventricular Arrhythmias

NICHOLAS Z. KERIN, ROGER D. BLEVINS, HOWARD FRUMIN, KATHY FAITEL, and MELVYN RUBENFIRE

To determine whether combined intravenous (i.v.) and oral loading with amiodarone can shorten its onset of action, a comparative study was conducted. Twenty patients with refractory ventricular arrhythmias were referred for treatment with amiodarone. Ten patients (group A) were treated with oral loading (800 mg/day for 7 days, 600 mg/day for 3 days and then 200 to 400 mg/day), and 10 patients (group B) were treated first with i.v. loading (5 mg/kg) and then by the same regimen as group A. The time to optimal ventricular arrhythmia control was shorter for group B (20 ± 18 vs 105 ± 83 days, $p < 0.05$) and the cumulative amiodarone dose at the time of control was smaller for group B (10 ± 8 vs 48 ± 39 g, $p < 0.05$). Thus, initial loading with i.v. amiodarone can shorten the time to optimal ventricular arrhythmia control.

92 Intravenous Quinidine: Relations Among Concentration, Tachyarrhythmia Suppression and Electrophysiologic Actions with Inducible Sustained Ventricular Tachycardia

HENRY J. DUFF, D. GEORGE WYSE, DANTE MANYARI, and L. BRENT MITCHELL

Twenty-one patients with sustained inducible ventricular tachycardia received a quinidine sulfate infusion designed to produce pseudo-steady-state concentrations in the low and high therapeutic range, avoiding high peak concentrations. Mean concentrations produced approximated the target levels (12.6 ± 11 and then 18 ± 9 μM/liter); however, there was substantial interindividual variability. Transient hypotension occurred in 3 patients, none of whom had marked impairment of left ventricular ejection fraction. Inducible ventricular tachycardia was suppressed in 5 patients at low concentrations and in an additional 4 at high concentrations. Response to intravenous quinidine did not predict similar response during oral therapy. This discrepancy was at least in part a result of poor patient tolerance of high-dose oral quinidine.

98 Effect of the Calcium Antagonist Diltiazem on Atrioventricular Conduction in Chronic Atrial Fibrillation

KARL THEISEN, MATHIAS HAUFE, JOCHEN PETERS, FRANZ THEISEN, and HANS JAHRMÄRKER

Mean ventricular rates and RR-interval histograms were analyzed in 10 patients with stable atrial fibrillation after a single dose of diltiazem and during maintenance therapy. Diltiazem reduced the mean ventricular rate significantly in these patients. Two distinct types of changes were found in the RR-interval histograms, suggesting that in 50% of the patients the increase of the concealed conduction in the atrioventricular node was primarily the result of an increase in the atrial fibrillation rate; however, in the other 50% both prolonged atrioventricular refractory period and increased atrial fibrillation rate contributed to the increase of concealed conduction.

Continued on page A35

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CARDIZEM®
(diltiazem HCl)

balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

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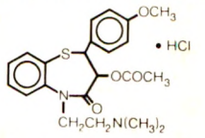
PROFESSIONAL USE INFORMATION

cardizem® (diltiazem HCl)

30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50} s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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PHARMACEUTICAL DIVISION
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103 Electrocardiographic Diagnosis of Left Ventricular Hypertrophy in the Presence of Left Bundle Branch Block: An Echocardiographic Study

HENRYK KAFKA, GARY W. BURGGRAF, and JOHN A. MILLIKEN

M-mode echocardiography was used to estimate the left ventricular (LV) mass of 100 subjects with left bundle branch block. A calculated LV mass of at least 215 g and an LV mass index of at least 115 g/m^2 of body surface area were used as standards for increased LV mass (LV hypertrophy). Fifty-six percent had LV hypertrophy by mass alone and 71% by LV mass index. Four electrocardiographic parameters—R in aVL ≥ 11; QRS axis ≤ -40; $SV_1 + RV_5$ or $RV_6 \geq 40$; $SV_2 \geq 30$ and $SV_3 \geq 25$—used in cumulative fashion had a sensitivity of 73% and 75% and a specificity of 66% and 90%, respectively. The electrocardiographic criteria for LV hypertrophy in left bundle branch block are at least as reliable as in normal conduction.

SYSTEMIC HYPERTENSION

107 Serial Measurements of Systolic Time Intervals During Treatment with Hydrochlorothiazide Alone and Combined with Other Antihypertensive Agents

MARY C. KYLE and EDWARD D. FREIS

The major changes in systemic time intervals after administration of hydrochlorothiazide were a decrease in left ventricular ejection time corrected for heart rate and electromechanical systole and an increase in preejection period/left ventricular ejection time. Addition of either hydralazine, prazosin, oxprenolol or propranolol resulted a partial return of these values toward baseline. Although the return, indicating improvement in left ventricular performance, may have been due to the effects of the added drugs, it could also result from long-term hemodynamic changes associated with the diuretic drugs.

112 Enhanced 24-Hour Norepinephrine and Renin Secretion in Young Patients with Essential Hypertension: Relation with the Circadian Pattern of Arterial Blood Pressure

MICHAEL L. TUCK, NAFTALI STERN, and JAMES R. SOWERS

Arterial blood pressure (BP), plasma norepinephrine (NE) and plasma renin activity (PRA) levels were measured in 9 young normotensive subjects (mean age 24 ± 3 years) and 9 young patients with essential hypertension (mean age 29 ± 3 years) at 20-minute intervals over 24 hours. A distinct circadian rhythm was demonstrated for mean BP, NE and PRA in both groups. Circadian changes in mean BP correlated with NE in all subjects. Mean NE and PRA levels were higher in the hypertensive group throughout the 24-hour cycle, the differences being most accentuated during sleep. These findings provide evidence for increased basal sympathetic tone throughout the 24-hour cycle in young persons with essential hypertension.

116 Role of Prostaglandins in the Renal Handling of a Salt Load in Essential Hypertension

BRUNO TRIMARCO, ANTONIO DE SIMONE, ALBERTO CUOCOLO, BRUNO RICCIARDELLI, MASSIMO VOLPE, PAOLA PATRIGNANI, LUIGI SACCA, and MARIO CONDORELLI

Renal function and systemic hemodynamics were assessed in 10 hypertensive patients and in 10 age-matched normotensive subjects under control conditions and after a salt load either alone or combined with indomethacin or sulindac. Indomethacin was used as ubiquitous inhibitor of prostaglandin synthesis and sulindac was used to inhibit prostaglandin synthesis in all tissue except the kidney. The changes induced by the salt load were comparable in the 2 groups. However, after indomethacin, only hypertensive patients showed a significant reduction in the 24-hour sodium excretion; this reduction was significantly correlated with the changes in renal blood flow ($r = 0.803$, $p < 0.01$). After the addition of sulindac to the salt load, the differences in the 24-hour sodium excretion between the 2 groups vanished. Our data suggest that renal prostaglandins participate in renal disposal of a chronic salt load in hypertensive patients but not in normal persons.

CONGESTIVE HEART FAILURE

122 Immediate Converting-Enzyme Inhibition with Intravenous Enalapril in Chronic Congestive Heart Failure

SPENCER H. KUBO, ROBERT J. CODY, JOHN H. LARAGH, XAVIER E. PRIDA, STEVEN A. ATLAS, ZHUNG YUAN, and JEAN E. SEALEY

To test the hypothesis that intravenous enalapril is a useful pharmacologic probe of the renin angiotensin system, intravenous enalapril was administered to 9 patients with severe congestive heart failure. This produced abrupt and complete blockade of converting enzyme with peak effect at 30 minutes. Associated with the reduction of angiotensin II–mediated vasoconstriction, systemic vascular resistance decreased markedly and cardiac

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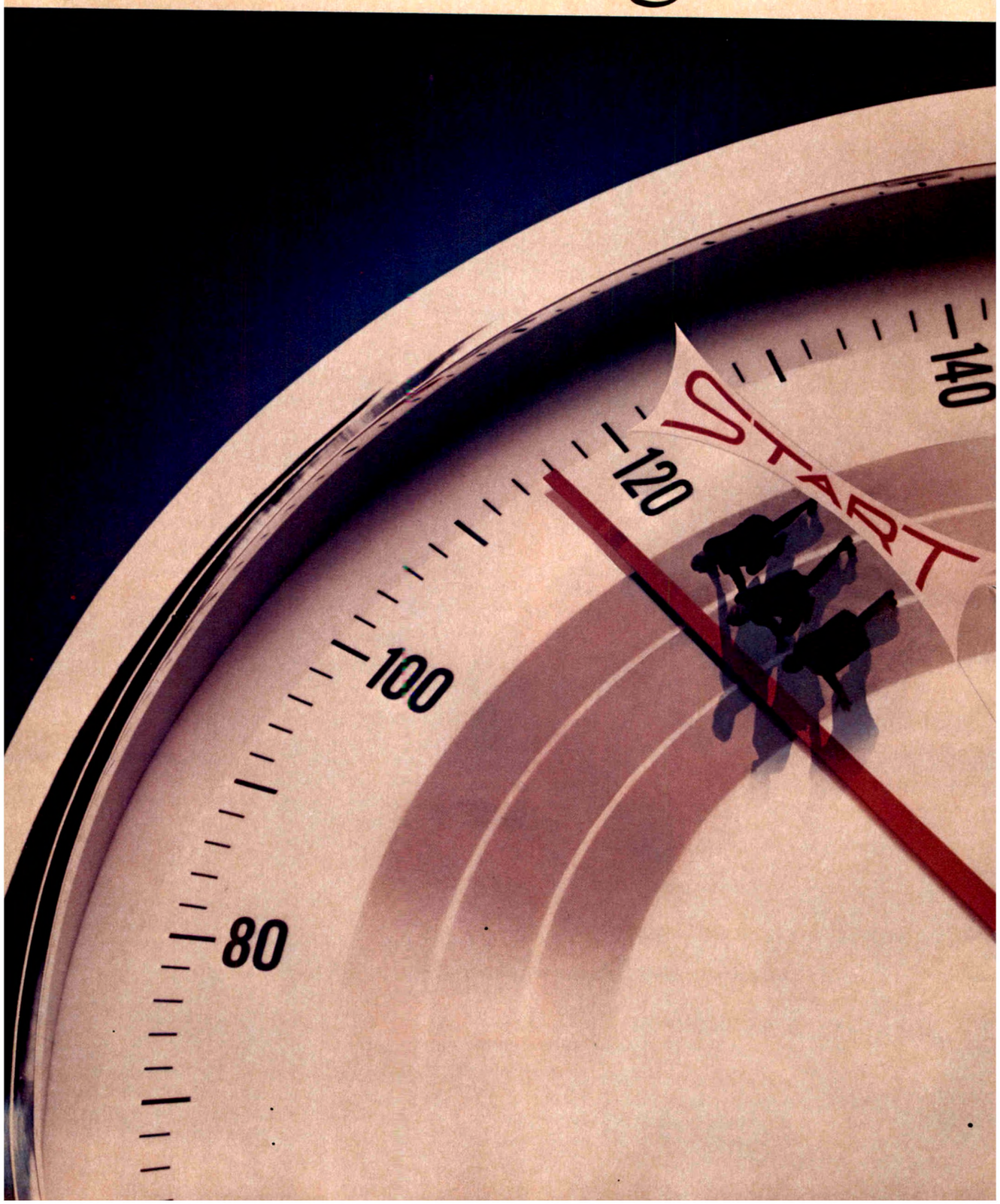
Initial therapy should
patients off right



start hypertensive

Minipress® for initial therapy
(prazosin HCl)

- Is effective when used alone
- Does not cause a significant incidence of sexual impotence, although it has been reported[1]
- Does not adversely affect blood lipids*[2]
- Does not lower heart rate, cardiac output or work capacity[3]
- Does not induce potassium wasting[4]
- The most common side effects with Minipress are: dizziness, headache, drowsiness, lack of energy, weakness, palpitations, nausea. With Minipress therapy there is a tendency for side effects to diminish with time. Syncope (sudden loss of consciousness) has been reported in about 0.15% of patients at an initial dose of 1 mg and in about 1% of patients at an initial dose of 2 mg

*Minipress is not indicated for the treatment of hyperlipidemia.

Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

for Initial Therapy in Hypertension

Please see Minipress brief summary on following page.

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Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

Brief Summary
MINIPRESS® (prazosin hydrochloride) Capsules ***For Oral Use***
INDICATIONS: MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
WARNINGS: Minipress may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120–160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution. (See DOSAGE AND ADMINISTRATION.) Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.
If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.
Patients should always be started on the 1 mg capsule of MINIPRESS. The 2 and 5 mg capsules are not indicated for initial therapy.
More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.
Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS in pregnancy has not been established. MINIPRESS is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of MINIPRESS in children.
ADVERSE REACTIONS: The most common reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.
The following reactions have been associated with MINIPRESS some of them rarely. (In some instances exact causal relationships have not been established.)
Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus, alopecia, lichen planus.
Genitourinary: urinary frequency, incontinence, impotence, priapism.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.
Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances the exact causal relationship has not been established because the baseline observations were frequently inadequate.
In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.
DOSAGE AND ADMINISTRATION: The dose of MINIPRESS should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:
Initial Dose: 1 mg two or three times a day. (See WARNINGS.)
Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.
Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.
OVERDOSAGE: Accidental ingestion of at least 50 mg of MINIPRESS in a two year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.
Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate MINIPRESS is not dialysable because it is protein bound.
TOXICOLOGY: Testicular changes, necrosis and atrophy have occurred at 25 mg/kg/day (60 times the usual maximum recommended dose of 20 mg per day in humans) in long term (one year or more) studies in rats and dogs. No testicular changes were seen in rats or dogs at the 10 mg/kg/day level (24 times the usual maximum recommended dose of 20 mg per day in humans). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS (prazosin hydrochloride) therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS (prazosin hydrochloride) alone for up to 51 months did not demonstrate changes in sperm morphology suggestive of drug effect.
HOW SUPPLIED: MINIPRESS is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).
More detailed information available on request.

References: 1. Lipson LG, Moore D, Pope AM et al: Sexual dysfunction in hypertensive diabetic men. *J Cardiovasc Med* (special suppl), April 1981, pp 30-37. **2.** Adapted from Kaplan NM: Summary. *J Cardiovasc Pharmacol* 4 (suppl 2): S265, 1982. **3.** Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in Prazosin Clinical Symposium Proceedings. Published as a special report by *Postgraduate Medicine*, New York, McGraw-Hill Book and Education Services Group, 1975, pp 45-52. **4.** Pitts NE: The clinical evaluation of prazosin, a new antihypertensive agent, in Prazosin Clinical Symposium Proceedings. Published as a special report by *Postgraduate Medicine*, New York, McGraw-Hill Book and Education Services Group, 1975, pp 117-127.

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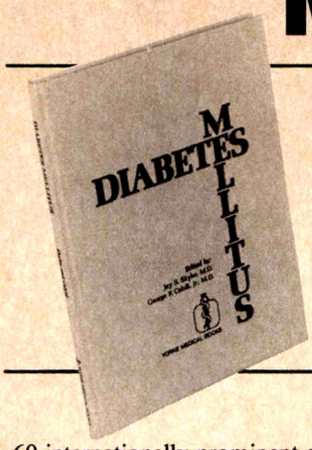
DIABETES MELLITUS



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index increased. The time course of angiotensin II levels suggested that the lack of a cumulative effect from additive doses was a result of complete inhibition of converting enzyme. One patient did not respond to treatment with enalapril, despite comparable hemodynamic severity of heart failure, the renin angiotensin system was not activated. Thus, intravenous enalapril is capable of rapid and complete inhibition of converting enzyme for the accurate assessment of angiotensin II–mediated vasoconstriction in severe congestive heart failure. This may be helpful in clarifying the pathophysiologic characteristics of vasoconstriction for more specific therapy.

VALVULAR HEART DISEASE

127 Pattern of Left Ventricular Diastolic Filling in Chronic Aortic Regurgitation: A Gated Blood Pool Assessment

STEVEN J. LAVINE, WILLIAM P. FOLLANSBEE, DAVID P. SHREINER, VENKATARAMAN KRISHNASWAMI, P. S. REDDY, and KAREN S. McKEE

The left ventricular diastolic filling curve was evaluated in 24 normal subjects and 29 patients with chronic aortic regurgitation (AR). Reduced peak filling rates (PFR), mean filling rates (MFR), peak ejection rates (PER), PFR/MFR, PFR/PER, and a longer rapid filling period normalized for diastolic time was noted in patients with AR. Eight of the 29 patients with AR had clinical evidence of congestive heart failure. Diastolic filling values were abnormal in this subgroup compared with those in normal subjects, but were similar to those in the asymptomatic subgroup of patients with AR. In patients with AR, an abnormal pattern of diastolic filling was noted, consisting of reduced diastolic filling and systolic ejection rates with more linear filling (reduced PFR/MFR) during a longer rapid filling period.

133 Frequency of Mitral Valve Dysfunction from Mitral Anular Calcium as Detected by Doppler Echocardiography

ARTHUR J. LABOVITZ, JEANNE G. NELSON, DENISE M. WINDHORST, HAROLD L. KENNEDY, and GEORGE A. WILLIAMS

Fifty-one patients with echocardiographic diagnosis of mitral anular calcification (MAC) were examined by Doppler echocardiography to determine the prevalence of mitral regurgitation (MR) and functional mitral stenosis. Eleven patients (22%) were found to have mild MR, 17 patients (33%) moderate to severe MR, and 4 patients (8%) had significant mitral stenosis. Clinical descriptors such as heart murmur and history of congestive heart failure were of limited value in predicting hemodynamic abnormalities. Evaluation of transmitral flow by Doppler of patients with mitral anular calcium may be a useful adjunct in the noninvasive assessment of mitral valve flow.

138 Mitral Valve Prolapse and Ruptured Chordae Tendineae

ROBERT M. JERESATY, JESSE E. EDWARDS, and SURENDRA K. CHAWLA

To determine the causes of ruptured chordae tendineae and their possible etiologic relation to mitral valve prolapse, the mitral valve was examined in 25 consecutive and surgically proved cases of ruptured chordae tendineae. Mitral valve prolapse, in the absence of endocarditis, was the underlying pathologic abnormality in 22 of these 25 patients (88%). In 4 patients, mitral valve prolapse had been documented by auscultation before chordal rupture; none of these patients had had infective endocarditis. The morphologic and historical evidence suggests that mitral valve prolapse is probably the most common cause of ruptured chordae tendineae.

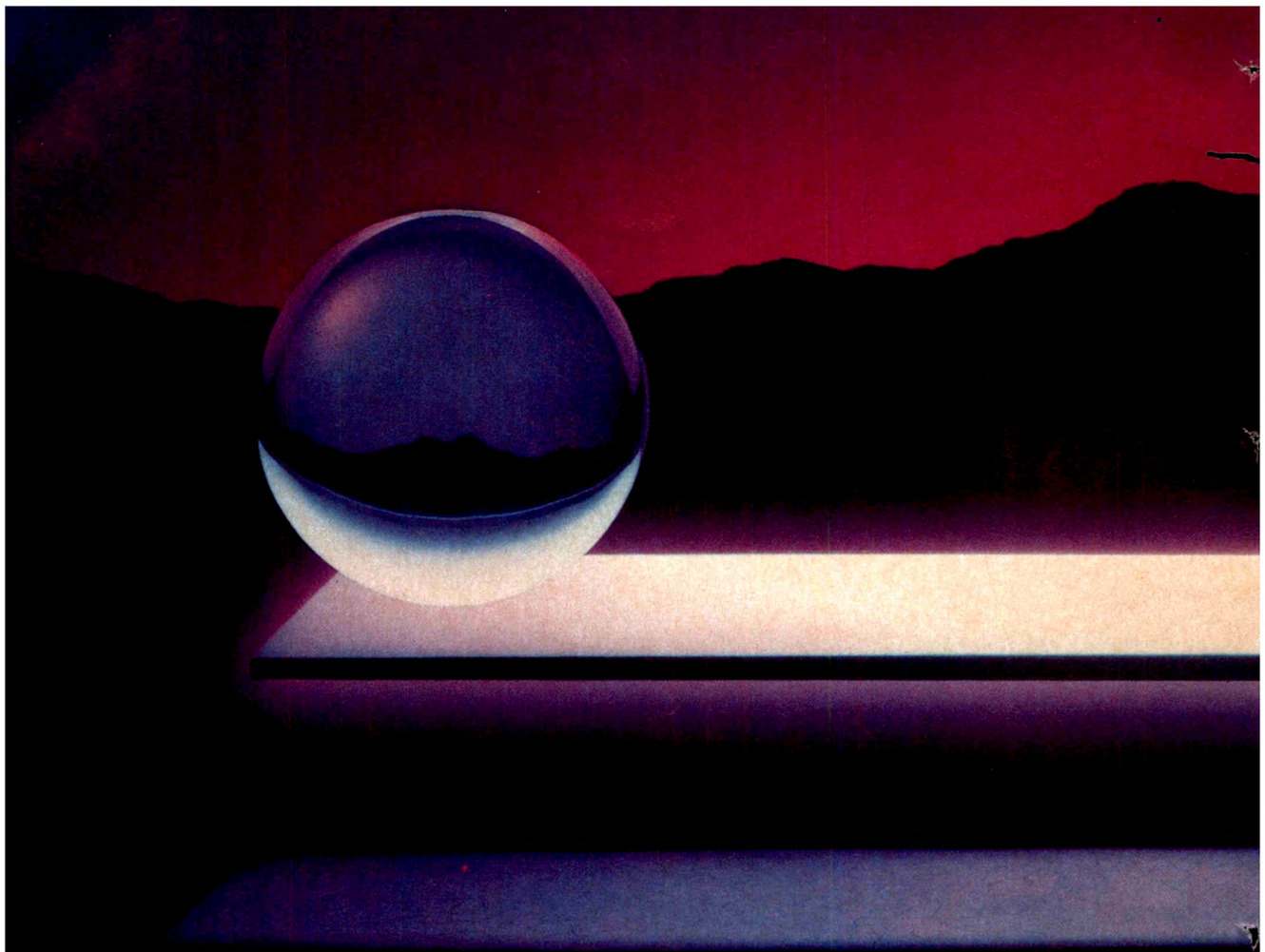
CARDIOMYOPATHY

143 Findings on Endomyocardial Biopsy in Infants and Children with Dilated Cardiomyopathy

ALAN B. LEWIS, HARRY B. NEUSTEIN, MASATO TAKAHASHI, and PAUL R. LURIE

Fifteen infants and children with dilated cardiomyopathy (DC) underwent transvascular endomyocardial biopsy. The light and electron microscopic findings were reviewed to assess the presence of lymphocytic infiltration indicating active myocarditis. Thirteen patients underwent both right and left ventricular biopsy and 2 underwent only right ventricular biopsy. An average of 5 tissue samples were obtained from each child. None of the endomyocardial biopsy specimens revealed an inflammatory process, despite evidence of extensive interstitial fibrosis, myofiber degeneration or hypertrophy. Ultrastructural changes in the mitochondria, T tubules or Z-band configuration were noted in approximately one-third of the patients. Thus, persistent, active myocarditis is an uncommon cause of DC in children. Immunosuppressive therapy, which may be harmful, should be considered in children with DC only after myocardial inflammation has been documented by endomyocardial biopsy.

Continued on page A44



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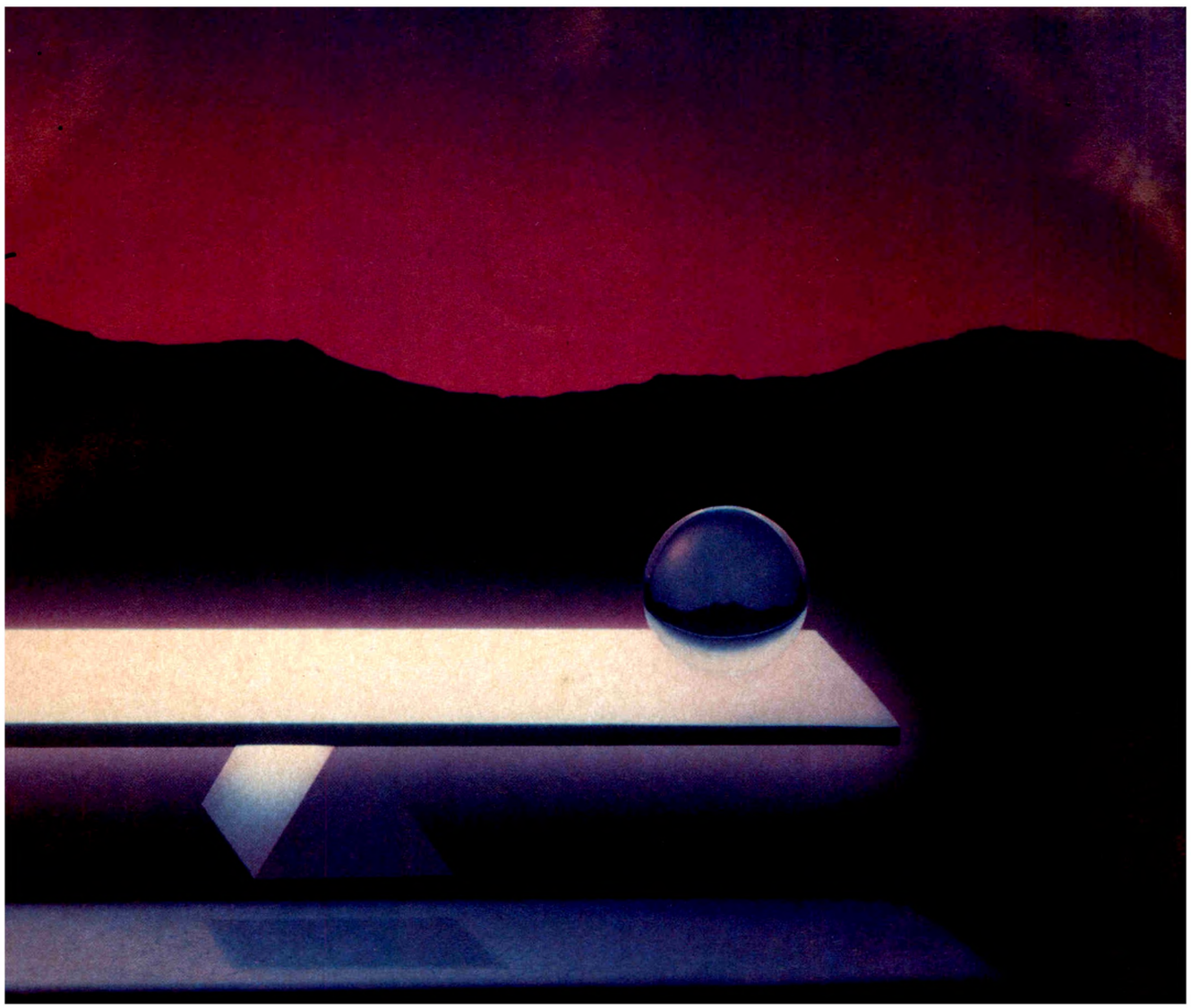

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A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO
		Total	VLDL	LDL	HDL	HDL Cholesterol / Total Cholesterol
IIa	−44%	−4.2%	−44.3%	− 5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	− 6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (see WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria
Central Nervous System: headache, dizziness, blurred vision
Musculoskeletal: painful extremities
Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:
Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia
Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints
Central Nervous System: vertigo, insomnia, paresthesia, tinnitus
Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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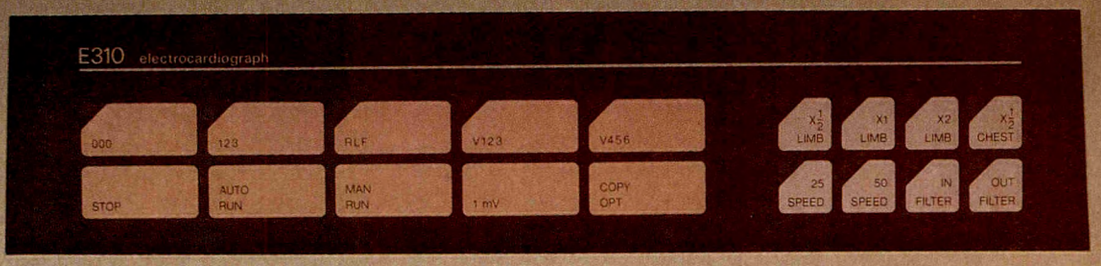

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146 **Arrhythmias in Ischemic and Nonischemic Dilated Cardiomyopathy: Prediction of Mortality by Ambulatory Electrocardiography**

JOHN HOLMES, SPENCER H. KUBO, ROBERT J. CODY, and PAUL KLIGFIELD

The prognostic value of the frequency and complexity of ventricular ectopy was evaluated in 31 patients with severe ischemic and nonischemic dilated cardiomyopathy who underwent right-sided cardiac catheterization and neurohormonal profiling. Subgroups based on peak ventricular arrhythmia grade included 9 patients with simple ventricular premature contractions (Lown 1 to 3) and 22 patients with complex ventricular premature contractions (Lown 4 and 5). During the 14-month mean follow-up period, 14 patients died, 12 from sudden death and 2 in circulatory failure. Mortality was strikingly related to arrhythmias: The mortality rate was 11% in the simple ventricular arrhythmia group and 59% in the complex ventricular arrhythmia group. No baseline variable other than peak ventricular premature contraction grade so clearly predicted death. These data are consistent with the hypothesis that complex ventricular arrhythmias represent an independent mortality risk factor in patients with severe dilated cardiomyopathy.

CONGENITAL HEART DISEASE

152 **Value of Image Enhancement and Injection of Contrast Medium for Right Ventricular Volume Determination by Two-Dimensional Echocardiography in Congenital Heart Disease**

PETER E. LANGE, PETER A. SEIFFERT, FRANK PREIS, ARMIN WESSEL, DIETRICH G. W. ONNASCH, HANS-J. HAHNE, and PAUL H. HEINTZEN

Right ventricular volumes calculated on the basis of echocardiographic cross sections from 23 children before and after application of digital enhancement techniques underestimated angiocardiographic volumes ($p < 0.01$) and more so in end-diastole (51%) than in end-systole (36%). Correlation between angio- and echocardiographic volumes was good for end-diastole and end-systole for the unprocessed echograms ($r = 0.97/0.95$), after image enhancement ($r = 0.97/0.96$), and after image enhancement and injection of contrast media ($r = 0.97/0.95$). The echocardiographic 4-chamber view allows right ventricular volume determination with an acceptable accuracy; its underestimation is related to inadequate visualization of trabeculations and mainly to the model used. Application of image enhancement techniques allows easier outlining of the internal cavity surface but does not improve the accuracy significantly. The advantage gained by the combination of contrast injection and image enhancement techniques does not warrant the routine central injection of available contrast material.

MISCELLANEOUS TOPICS

159 **Magnitude and Implications of Spontaneous Hemodynamic Variability in Primary Pulmonary Hypertension**

STUART RICH, GILBERT E. D'ALONZO, DAVID R. DANTZKER, and PAUL S. LEVY

The pulmonary artery (PA) pressure at rest and pulmonary resistance may vary in patients with primary pulmonary hypertension (PPH). We determined the amount of variability (coefficient of variation) in the systemic and PA pressure, cardiac output and systemic and pulmonary resistance by making hourly measurements for 6 hours in 12 patients with PPH. Then, the patients underwent hydralazine and nifedipine treatment and the percent decrease in pulmonary resistance was measured. Spontaneous variability occurred in every patient, averaging 8% in PA pressure and 13% in pulmonary resistance. Patients with the most variability in PA pressure had the most variability in cardiac output ($r = 0.69$, $p = 0.02$) and variability was greatest in patients who had the highest pulmonary resistances ($r = 0.91$, $p < 0.01$). There was no correlation between the amount of variability and the decrease in pulmonary resistance from hydralazine or nifedipine. From these data, we derived 95% confidence limits and calculated that a change of 22% in PA pressure, or 36% in pulmonary resistance would be necessary in order to attribute the changes to a drug effect in a given patient.

164 **Acute Effects of Alcohol on Left Ventricular Function in Healthy Subjects at Rest and During Upright Exercise**

HENNING KELBAEK, THOMAS GJØRUP, INGELISE BRYNJOLF, NIELS JUEL CHRISTENSEN, and JOHN GODTFREDSEN, *With the technical assistance of* BIRGIT VESTERGAARD

Radionuclide angiocardiography was performed in 6 healthy men, median age 25 years, at rest and at submaximal exercise during light (serum ethanol 23 mmol/liter) and heavy (serum ethanol 45 mmol/liter) alcohol intoxication. At light intoxication, left ventricular ejection fraction at rest decreased (5%). At heavy intoxication left ventricular ejection fraction decreased both at rest (11%) and at 75% submaximal exercise (6%), heart rate at rest increased (81 vs 62 beats/min), and systolic blood pressure decreased at 50% submaximal exercise (145 vs 163 mm Hg). Plasma-norepinephrine concentrations were increased by 24% during light and by 30 to 38% during heavy intoxication; no changes were recorded in plasma epinephrine concentrations. Control investiga-

Continued on page A50

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PREDICTABILITY IN A B.I.D. DOSAGE

Norpace® CR

(disopyramide phosphate)

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The most commonly seen side effects of disopyramide phosphate are anticholinergic, and the most severe are due to its negative inotropic properties.

Please see next page for a brief summary of the complete prescribing information.

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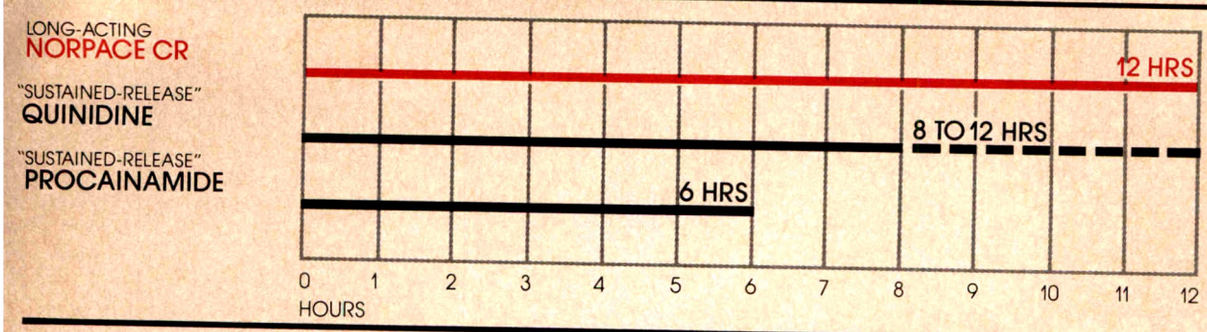
PREDICTABILITY IN A B.I.D. DOSAGE

DURATION OF ANTIARRHYTHMIC ACTION



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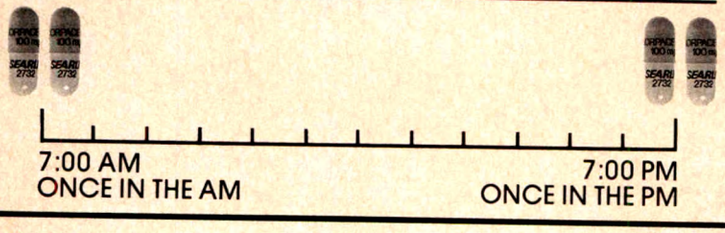

Brief Summary

Before prescribing, please consult current complete prescribing information, a summary of which follows: **Indications:** For suppression and prevention of recurrence of the following cardiac arrhythmias: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Norpace CR should not be used initially if rapid establishment of disopyramide plasma levels is desired. Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace or Norpace CR should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patients should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Therefore, a loading dose of Norpace should not be given to such patients, and initial dosage and subsequent dosage adjustments should be made under close supervision. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Concomitant administration of disopyramide phosphate with phenytoin or other hepatic enzyme inducers may cause lower disopyramide plasma levels. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention especially in males with benign prostatic hypertrophy, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

Revised 10/84 • 4J64V

J68T

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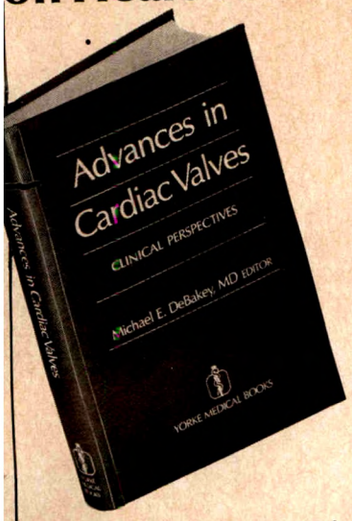

Advances in Cardiac Valves
Clinical Perspectives

edited by **Michael E. DeBakey, MD**

0-914316-40-0, November 1983, 274pp., $35.00

This valuable new clinical reference provides a detailed update on many aspects of mechanical heart valve prostheses, including hemodynamics, clinical results, results in children, non-invasive assessments, special indications, and implant techniques. Each topic is presented in an easily understood style and format which facilitate the comprehension of recent developments in heart valve replacement for the busy clinician.

Each chapter is written by internationally respected physicians and medical scientists each of whom is pre-eminent in his field. All of this information has been co-ordinated by Dr. DeBakey to produce a very readable and informative volume on the state-of-the-art of heart valve replacement with mechanical prostheses. No cardiologist, cardiovascular surgeon, internist, or bioengineer can afford *not* to be knowledgeable about th information in this book.

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CONTRIBUTORS INCLUDE

Mauro Abbate
Franz W. Amann
Manuel J. Antunes
Kit V. Arom
P. Barzellotti
Enrico Baruffi
Giuseppe Battaglia
Eugene M. Baudet
Marco Benedetti
Dieter Burckhardt
Jorge L. Camunas
R. Carlier
E. Stanley Crawford
Luigi C. D'Alessandro
Michael E. DeBakey
Doriano DeLuca
Phillipe Despins
Frank E. Deuvaert
Maria Diaz
P. Di Francesco
C. Doutremepuich
Henri Dupon
D. Duveau
Robert Emery
Manuel R. Estioko
F. Fabbrizzi
Rocco Gallo
Maurizio Gentile
Carl C. Gill
Filippo Giordano
Erich Grädel
Richard J. Gray
Joachim Hasse
Andreas Hoffmann
Dieter Horstkotte
Jimmy F. Howell
Roy A. Jurado
Robert B. Karp
Thomas E. Kersten
Robin H. Kinsley
Reiner Körfer
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J. L. Michaud
Bruce P. Mindich
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Orazio Monaco
George C. Morris
Angelo Moschetto
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F. Ortisi
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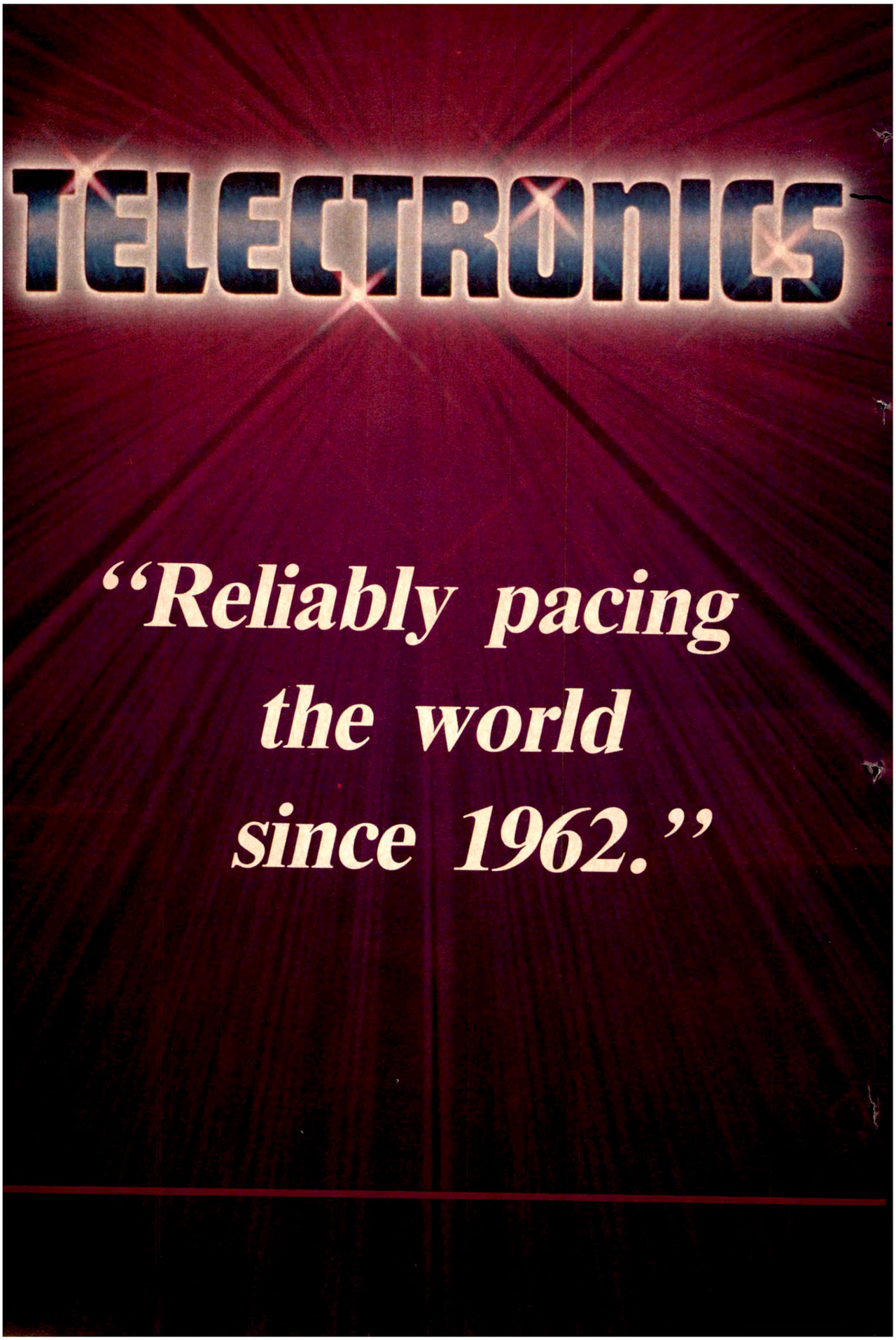
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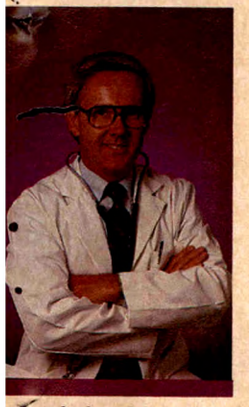

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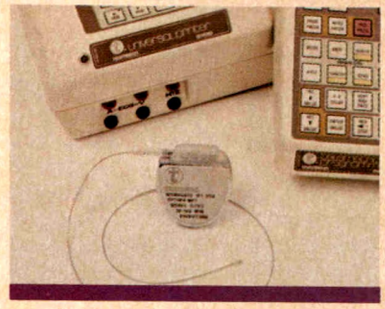

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a member of the NUCLEUS group

tions revealed no significant changes in measurements due to ingestion of isovolumic, isocaloric drinks. It is suggested that alcohol intoxication causes a dose-dependent impairment of cardiac contractility. Compensatory mechanisms may account for a reduced influence during exercise.

168 **Diastolic Time During Recovery from Upright Exercise in Persons Without Heart Disease**

TETSURO SUGIURA, TOSHIJI IWASAKA, YOSHINORI L. DOI, BRUCE G. HAFFTY, MITSUO INADA, and DAVID H. SPODICK

In 12 normal volunteers, despite decreased heart rate at 5 and 2 minutes after exercise in the upright position, diastolic time and total diastole per minute shortened significantly, with disproportionate lengthening of diastolic time at 2 minutes. These events appear to represent a physiologic response due to increased ventricular filling in the presence of diminishing adrenergic effect.

171 **Radiation Exposure and Protection in Cardiac Catheterization Laboratories**

STEPHEN W. MILLER and FRANK P. CASTRONOVO, Jr.

This report is a review of the literature regarding radiation exposure and protection in cardiac catheterization laboratories. Cardiac catheterization with angiography may give a patient the largest dose of x-radiation of any diagnostic medical examination. In contrast, the physicians and technologists working daily in the catheterization laboratory receive low-level radiation over an extended time period. Although the radiobiology is complex, the physicians who perform cardiac catheterization should be familiar with potential genetic and somatic effects and with the methods to reduce or eliminate radiation exposure. Catheterization personnel have control over the time duration of exposure, placement of technologists, shielding and dosimetry.

METHODS

177 **Accuracy of Left Ventricular Ejection Fraction Using the Nuclear Stethoscope in Left Ventricular Aneurysm**

DAVID M. McCARTHY and P. TODD MAKLER, Jr.

Although the nuclear stethoscope, a nonimaging probe, accurately determines left ventricular (LV) ejection fraction (EF), its reliability in patients with LV aneurysm has not been established. Accordingly, LVEF was determined using the nuclear stethoscope and compared with that determined by equilibrium gated blood pool scanning in 29 patients, 1 studied on 2 separate occasions, for a total of 30 patient studies. Patient studies were separated into 2 groups. Patients in group I ($n = 20$) had no gated blood pool evidence for aneurysm, and those in group II ($n = 10$) had discrete focal akinesia or dyskinesia. Nineteen patients (13 in group I and 6 in group II) had 2 separate nuclear stethoscope acquisitions. In group I, EF determined by gated blood pool scanning ($53 \pm 4\%$, mean $\pm$ standard error) did not differ from that determined by nuclear stethoscope ($51 \pm 4\%$). EF determined using either gated blood pool scanning ($32 \pm 6\%$) or nuclear stethoscope ($35 \pm 5\%$) was significantly lower in group II than in group I, although nuclear stethoscope and gated blood pool scanning did not differ. Reproducibility was excellent ($r = 0.96$). Overall, nuclear stethoscope and gated blood pool EFs correlated closely ($r = 0.93$), and the correlation coefficients were similar in groups I ($r = 0.92$) and II ($r = 0.92$). The slopes of the regression curve for group I (0.97) and group II (0.92) were not statistically different. These results confirm the accuracy and reproducibility of LVEF determination by nuclear stethoscope and specifically demonstrate its reliability in patients with LV aneurysm.

CARDIOVASCULAR PHARMACOLOGY

181 **Association of Methemoglobinemia and Intravenous Nitroglycerin Administration**

KERRY J. KAPLAN, MARK TABER, J. RUSSELL TEAGARDEN, MICHELE PARKER, and RICHARD DAVISON

Significant elevation of arterial methemoglobin levels has been reported with the administration of intravenous (i.v.) nitroglycerin (NTG). To determine the incidence and clinical significance of this potential side effect of i.v. NTG, serial arterial methemoglobin levels were determined in 50 consecutive patients who received i.v. NTG for at least 48 hours. The mean methemoglobin level for the 141 samples was $1.57 \pm 0.08\%$, which differs from the control mean value in our laboratory of $0.44 \pm 0.01\%$. Although no patients had clinical symptoms from methemoglobin, 20 patients had elevated levels ($>1\%$) on at least 1 occasion. Seventy-eight of the 141 samples analyzed were in the normal range, whereas the other 63 determinations were between 2 and 5%. Patients with normal methemoglobin levels differed from those with abnormal levels in the dose of i.v. NTG (mean infusion rate 244 ± 16 vs 351 ± 17 μg/min; total cumulative dose $1,612 \pm 153$ vs $3,398 \pm 308$ mg). In conclusion, clinically significant methemoglobinemia is uncommon with i.v. NTG infusion; however, when large doses of NTG are administered, this complication is more likely.

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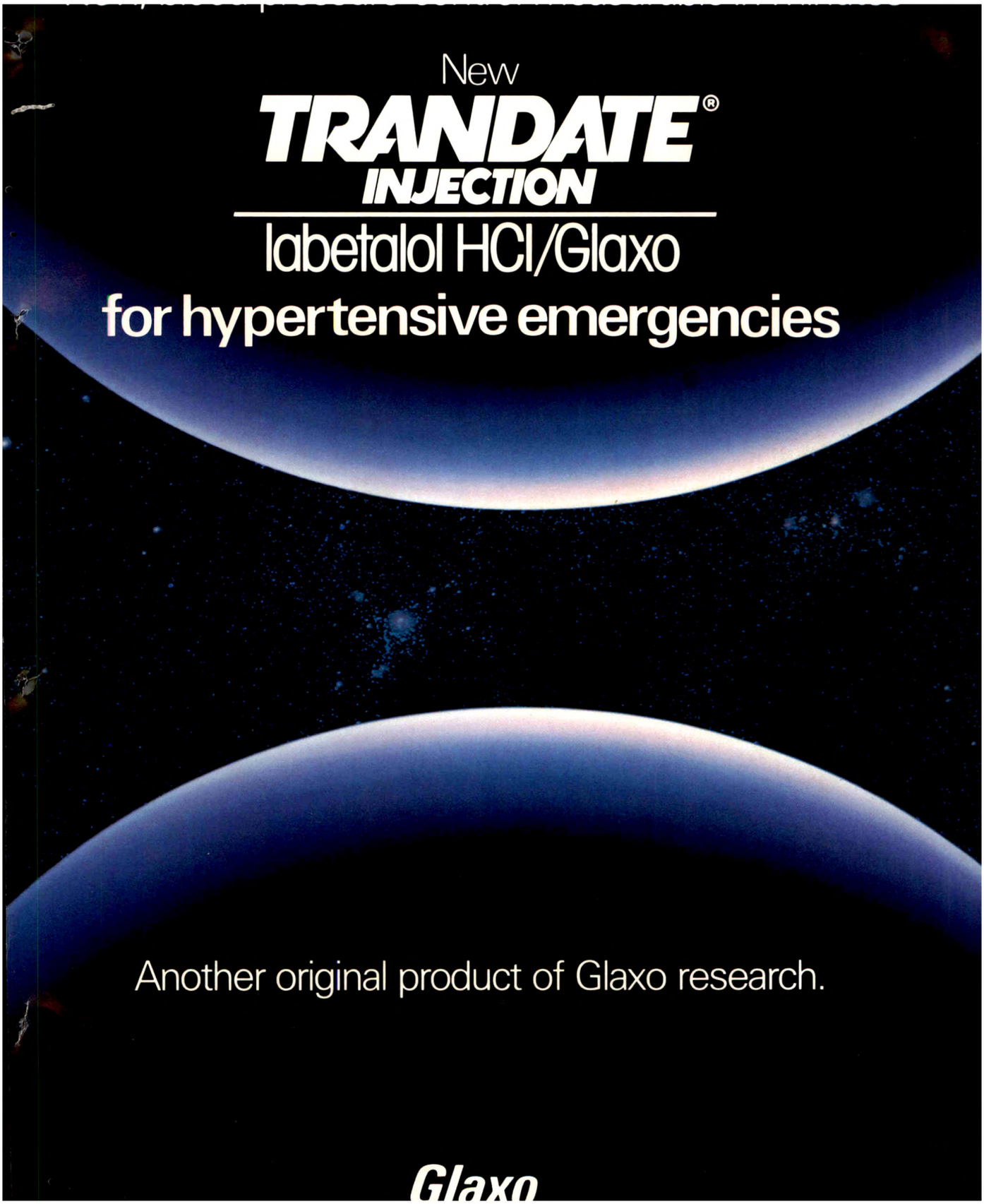
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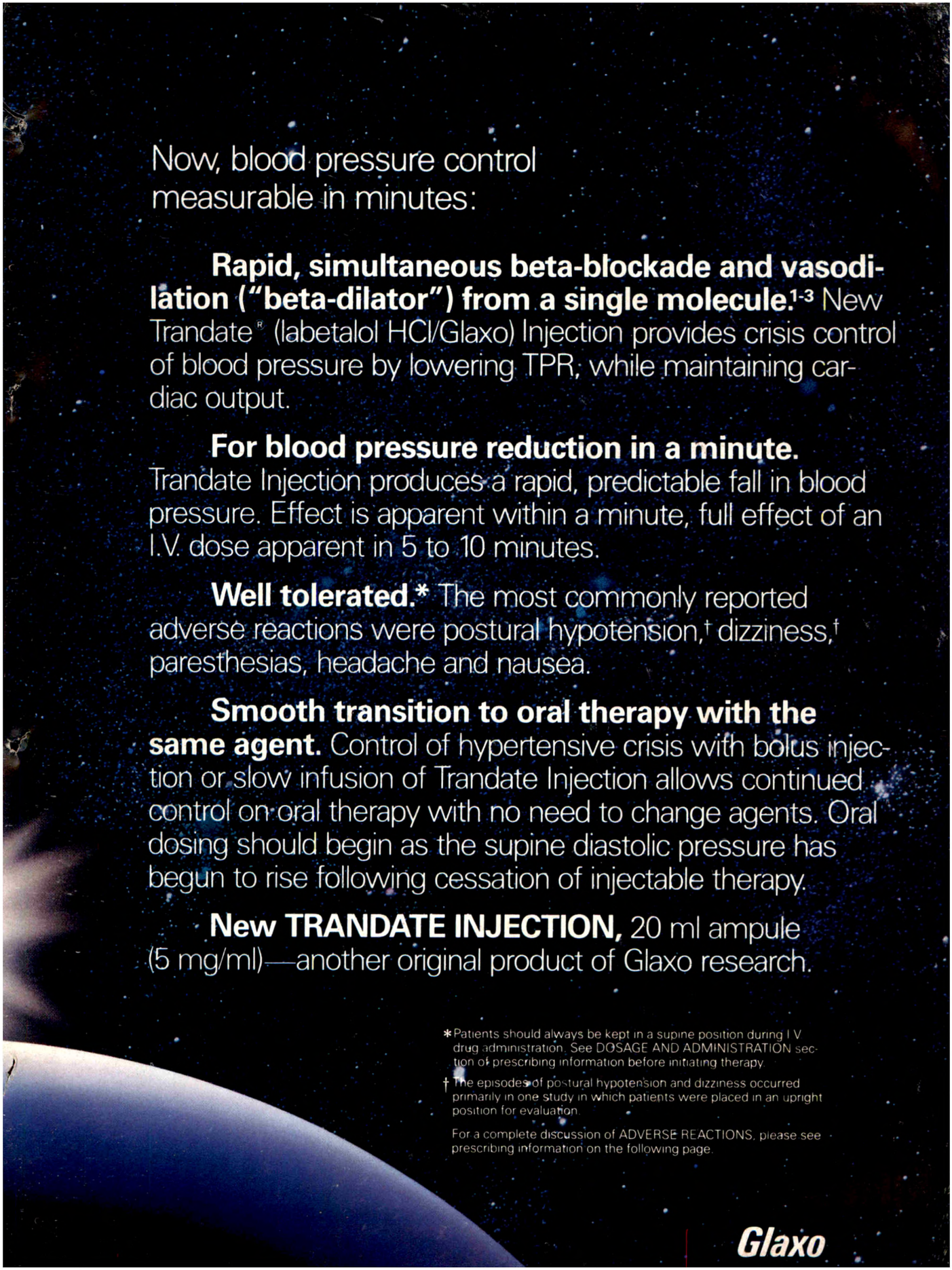
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New TRANDATE INJECTION, 20 ml ampule (5 mg/ml)—another original product of Glaxo research.
*Patients should always be kept in a supine position during I.V. drug administration. See DOSAGE AND ADMINISTRATION section of prescribing information before initiating therapy.
† The episodes of postural hypotension and dizziness occurred primarily in one study in which patients were placed in an upright position for evaluation.
For a complete discussion of ADVERSE REACTIONS, please see prescribing information on the following page.
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TRANDATE® Injection
(labetalol hydrochloride)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

TRANDATE® (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.

CONTRAINDICATIONS

TRANDATE® (labetalol HCl) Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS

Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TRANDATE® (labetalol HCl) therapy should be withdrawn (gradually, if possible).

Ischemic Heart Disease Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TRANDATE (labetalol HCl) is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Since TRANDATE (labetalol HCl) Injection at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

Pheochromocytoma Intravenous labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta blockade also reduces the release of insulin in response to hypoglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see Drug Interactions under PRECAUTIONS).

Rapid Decreases of Blood Pressure Caution must be observed when reducing severely elevated blood pressure. Although such findings have not been reported with intravenous labetalol HCl, a number of adverse reactions, including cerebral infarction, optic nerve infarction, angina and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours, to as long as one or two days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

PRECAUTIONS

General *Impaired Hepatic Function* may diminish metabolism of TRANDATE® (labetalol HC., Injection.

Hypotension Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE (labetalol HCl) Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

Jaundice or Hepatic Dysfunction On rare occasions, oral labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately, should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) TRANDATE (labetalol HCl) Injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on TRANDATE Tablets, following adequate control of blood pressure with TRANDATE Injection, appropriate directions for titration of dosage should be provided. (see DOSAGE AND ADMINISTRATION).

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted: While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests

Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

Since TRANDATE (labetalol HCl) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE® (labetalol HCl) Injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

TRANDATE® (labetalol HCl) Injection is usually well tolerated. Most adverse effects have been mild and transient and in controlled trials involving 92 patients did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE (labetalol HCl) Injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with TRANDATE (labetalol HCl) Injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.

Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin 7; hypoesthesia (numbness), and vertigo 1 each.

Gastrointestinal System Nausea in 13; vomiting 4; dyspepsia and taste distortion, 1 each.

Metabolic Disorders Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Psychiatric Disorders: Somnolence/yawning in 3.

Respiratory System: Wheezing in 1.

Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see TRANDATE Tablet Product Information for details). Certain of the side effects increased with increasing oral dose in the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose-related.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.

Clinical laboratory tests: Among patients dosed with TRANDATE (labetalol HCl) Tablets, there have been reversible increases of serum transaminases in 4% of patients tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with TRANDATE® (labetalol HCl) Injection causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia*—administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure*—administer a digitalis glycoside and a diuretic. *Hypotension*—administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm*—administer a beta$_2$-stimulating agent and/or a theophylline preparation.

If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

TRANDATE® (labetalol HCl) Injection is intended for intravenous use in hospitalized patients. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

Patients should always be kept in a supine position during the period of intravenous drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position should be established before permitting any ambulation, such as using toilet facilities.

Either of two methods of administration of TRANDATE Injection may be used: a) repeated intravenous injections, b) slow continuous infusion.

Repeated Intravenous Injection: Initially, TRANDATE (labetalol HCl) Injection should be given in a dose of 20 mg labetalol HCl (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow intravenous injection over a two-minute period.

Immediately before the injection and at five and ten minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 mg or 80 mg can be given at ten-minute intervals until a desired supine blood pressure is achieved or a total of 300 mg labetalol HCl has been injected. The maximum effect usually occurs within 5 minutes of each injection.

Slow Continuous Infusion: TRANDATE (labetalol HCl) Injection is prepared for intravenous continuous infusion by diluting the ampule contents with commonly used intravenous fluids (see below). Examples of two methods of preparing the infusion solution are:

The contents of two ampules (40 ml) are added to 160 ml of a commonly used intravenous fluid such that the resultant 200 ml of solution contains 200 mg of labetalol HCl, 1 mg/ml. The diluted solution should be administered at a rate of 2 ml/min to deliver 2 mg/min.

Alternatively, the contents of two ampules (40 ml) of TRANDATE (labetalol HCl) Injection can be added to 250 ml of a commonly used intravenous fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2 mg/3 ml. The diluted solution should be administered at a rate of 3 ml/min to deliver approximately 2 mg/min.

The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion, the diluted solution can be infused using a controlled administration mechanism, e.g., graduated burette or mechanically driven infusion pump.

Since the half life of labetalol is 5 to 8 hours, steady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should then be stopped and oral labetalol HCl started (see below). The effective intravenous dose is usually in the range of 50 to 200 mg. A total dose of up to 300 mg may be required in some patients.

Blood Pressure Monitoring: The blood pressure should be monitored during and after completion of the infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic blood pressure during intravenous treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as an indicator of effectiveness in addition to the response of the diastolic pressure.

Initiation of Dosing with TRANDATE (labetalol HCl) Tablets: Subsequent oral dosing with TRANDATE (labetalol HCl) Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 or 400 mg, depending on the blood pressure response. Thereafter, *inpatient titration with TRANDATE (labetalol HCl) Tablets* may proceed as follows:

Inpatient Titration Instructions

Regimen	Daily Dose*
200 mg b.i.d.	400 mg
400 mg b.i.d.	800 mg
800 mg b.i.d.	1600 mg
1200 mg b.i.d.	2400 mg

*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of TRANDATE Tablets may be increased at one day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing see TRANDATE (labetalol HCl) Tablets Product Information DOSAGE AND ADMINISTRATION for additional recommendations.

HOW SUPPLIED

TRANDATE® (labetalol HCl) Injection, 5 mg/ml, is supplied in 20 ml (100 mg) ampules, box of 1 (NDC 0173-0350-59).

Store between 2° and 30°C (36° and 86°F). Do not freeze.

Manufactured for Glaxo Inc., Research Triangle Park, NC 27709
by Schering Pharmaceutical Corporation (PR) Manati, PR 00701

Issued: August 1984

References

1. Michelson EL. Labetalol: a major pharmacologic departure. *Card Prod News* 1983; 3(6):1, 31-32. **2.** Wallin JD, O'Neill WM, Jr. Labetalol, current research and therapeutic status. *Arch Intern Med* 1983; 143:485-90. **3.** MacCarthy EP, Bloomfield SS. Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. *Pharmacotherapy* 1983; 3(4):193-219.

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184 Incomplete and Delayed Bioavailability of Sublingual Nitroglycerin

PATRICK K. NOONAN and LESLIE Z. BENET

Eight healthy male volunteers received 16 doses of sublingual nitroglycerin (GTN) tablets (0.4 mg). Each subject also received an i.v. GTN infusion so that the absolute bioavailability could be evaluated. The mean bioavailability (±SD) of sublingual GTN, estimated from plasma GTN concentrations, 36.2 ± 24.9% (range 2.6 to 113%). The amount of GTN not absorbed after 8 minutes, determined from the mouth rinse analyses, varied from 2.7 to 65.8% (mean 31.4 ± 18.9%) of the administered dose. A mean GTN peak concentration of 1.89 ± 1.64 ng/ml was attained. A mean peak time of 5.3 ± 2.3 minutes indicates that sublingual absorption is not instantaneous and can be relatively slow, with peak times of as long as 10 minutes. These data indicate that GTN pharmacokinetic values should not be estimated only from sublingual doses of GTN. Attempts to correlate pharmacodynamic measurements to sublingual doses must take into account the low and variable bioavailability and the potentially long peak times after sublingual GTN administration to patients.

EXPERIMENTAL STUDIES

188 Validation in Dogs of a Rapid Digital Angiographic Technique to Measure Relative Coronary Blood Flow During Routine Cardiac Catheterization

JOHN McB. HODGSON, VICTOR LeGRAND, ERIC R. BATES, G. B. JOHN MANCINI, FRED M. AUERON, WILLIAM W. O'NEILL, SANDRA B. SIMON, GLENN J. BEAUMAN, MICHAEL T. LeFREE, and ROBERT A. VOGEL

A digital angiographic technique that allows for rapid analysis of relative regional coronary blood flow using selective coronary arteriography is reported. Validation of this technique was performed in 14 instrumented dogs by comparison of digital flow ratio estimates with electromagnetic flow ratio measurements. Electrocardiographic gated digital images were acquired at baseline flow and during contrast or papaverine-induced hyperemia. Dual-parameter functional images were then generated using color and intensity coding to represent contrast medium arrival time and density, respectively. Coronary flow reserve ratios calculated digitally correlated well with actual electromagnetic flow ratios ($r = 0.92$). Digital estimates were accurate (regression slope = 0.90), reproducible (±13%) and had excellent interobserver ($r = 0.99$) and intraobserver ($r = 0.98$) variability. Thus, digital angiography can be used during routine cardiac catheterization to obtain rapid, accurate and reproducible estimates of relative regional coronary blood flow.

194 Electrophysiologic and Anatomic Changes in the Atrioventricular Junction of Dogs After Direct-Current Shocks Through Tissue Fixation Catheters

MELVIN M. SCHEINMAN, SAROJA BHARATI, YIN-SHI WANG, WILLIAM A. SHAPIRO, and MAURICE LEV

Tissue fixation electrode catheters were inserted under fluoroscopy into the region of atrioventricular (AV) node in 6 dogs and a series of shocks were delivered from the electrode catheter to a back patch. Electrophysiologic studies 2 to 3 weeks after the procedure showed only minimal changes in AV nodal conduction, whereas histologic examination showed substantial damage to the AV junction. It is concluded that there is a large safety margin for AV conduction. This technique may be applicable to patients with drug-refractory AV nodal reentrant tachycardia.

199 Mechanical "Cough" Cardiopulmonary Resuscitation During Cardiac Arrest in Dogs

JAMES T. NIEMANN, JOHN P. ROSBOROUGH, ROBERT A. NISKANEN, CLIF ALFERNESS, and J. MICHAEL CRILEY

Coughing produces systemic perfusion during ventricular fibrillation (VF). A circulatory assist apparatus was devised to reproduce the physiology of forceful coughing, i.e., simultaneous pulsatile increases in intrathoracic pressure (pneumatic vest) and intraabdominal pressure (abdominal binder). In this study, countershock outcome after 30 minutes of VF and CPR with the vest/binder device or conventional CPR are compared in 18 dogs. Aortic and right atrial (RA) pressures, the instantaneous aortic-RA difference (coronary perfusion pressure) and blood gas levels were measured. Only 1 of 9 dogs that received conventional CPR were resuscitated and survived 24 hours; 7 of 9 dogs supported with the vest/binder device were resuscitated and were neurologically normal at 24 hours ($p = 0.007$). Systolic aortic and RA pressures, mean coronary perfusion pressure, and blood gas levels were not significantly different between survivors and nonsurvivors. Peak diastolic coronary perfusion pressure averaged 23 ± 6 mm Hg for survivors, but only 6 ± 10 mm Hg for nonsurvivors ($p < 0.001$). It is concluded that (1) circulatory support techniques that use the "thoracic pump" can sustain vital organ perfusion during VF, and (2) diastolic coronary perfusion pressure is a determinant of countershock outcome and can be favorably manipulated by mechanical means.

Continued on page A56

205 **Influence of the Aortic Component of the Second Heart Sound on Left Ventricular Maximal Negative dP/dt in the Dog**

DAMON SMITH and ERNEST CRAIGE

Maximal negative left ventricular dP/dt is widely used as a measure of isovolumic muscular relaxation of the left ventricle. In the course of canine experiments designed to elucidate the hemodynamic events responsible for the aortic component of the second heart sound, high-fidelity left ventricular pressure and dP/dt signals were recorded, as well as accelerations detected on the root of the aorta and epicardium at the cardiac apex. The aortic component of the second heart sound was coincident with maximal negative dP/dt and affected its magnitude to a variable and unpredictable extent. This may account for some of the unexpected variations in magnitude of maximal negative dP/dt that have been described in various disease states as well as in laboratory experiments in which the effects of physiologic and pharmacologic interventions have been studied.

210 **Morphologic Changes Induced by Dilation of the Pulmonary Valve Anulus with Overlarge Balloons in Normal Newborn Lambs**

JOHN C. RING, THOMAS J. KULIK, BARBARA A. BURKE, and JAMES E. LOCK

The pulmonary valve anuli of 14 normal newborn lambs were dilated with angioplasty balloons 20% smaller to 90% larger than the anulus. In 3 dilations, a dynamic technique was used, consisting of withdrawal of the fully inflated balloon from the anulus into the body of the right ventricle. Twelve lambs were killed acutely, 2 were killed late, and detailed gross anatomic and microscopic observations of the heart were made. The major damage to the heart from balloon dilation is not to the pulmonary anulus, but to the right ventricular outflow tract and free wall, with mural hemorrhages of varying size. Trauma is minor if the balloon is less than 30% larger than the anulus, but is considerable when the balloon is more than 50% larger, and is worst subjacent to the proximal end of the balloon, so that longer balloons may cause greater damage. Resolution of acute right ventricular hemorrhage occurs with small, patchy areas of fibrosis.

EDITORIALS

215 **Potential Limitations of Quantitative Thallium Scanning**

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217 **On Pulmonary Vascular Resistance: The Need for More Precise Definition**

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224 **Thallium-201 Exercise Scintigraphy and Left Bundle Branch Block**

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226 **Effects of Noncaptured Stimuli During Rapid Right Ventricular Pacing: Does Concealed Conduction Occur in the Human Ventricle?**

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227 **Polymorphic Ventricular Tachycardia and Ventricular Fibrillation Due to N-Acetyl Procainamide**

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229 **Prosthetic Mitral Regurgitation Detected by Doppler Echocardiography**

ROBERT P. FERRARA, ARTHUR J. LABOVITZ, ROBERT D. WIENS, HAROLD L. KENNEDY, and GEORGE A. WILLIAMS

230 **Tissue Characterization by Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy**

DONALD FARMER, CHARLES B. HIGGINS, EDWARD YEE, MARTIN J. LIPTON, DENNIS WAHR, and THOMAS PORTS

Indications: Premature atrial and ventricular contractions, aproxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, paroxysmal ventricular tachycardia when not associated with complete heartblock, maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting in extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, light-headedness, and tremor; (3) G.I. symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at the rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

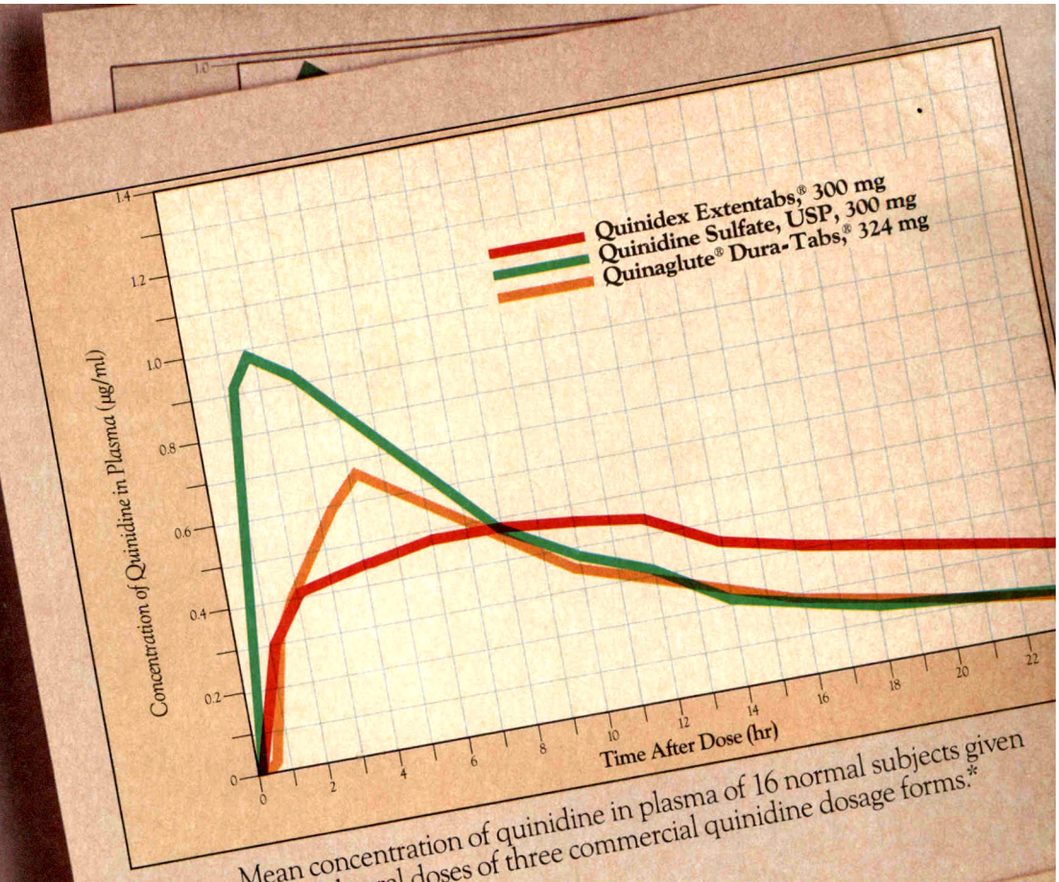
NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G.I. symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

Dosage: Two Quinidex Extentabs every 8 to 12 hours.

How Supplied: White sugar-coated Extentabs in bottles of 100 (NDC 0031-6649-63) and 250 (NDC 0031-6649-67) and Dis-co® Unit Dose Packs of 100 (NDC 0031-6649-64).

Rev. Dec. 1981



Mean concentration of quinidine in plasma of 16 normal subjects given single oral doses of three commercial quinidine dosage forms.*

Consider The Evidence For Quinidex (Quinidine Sulfate, USP), 300 mg Extentabs®

- The convenience of b.i.d. dosage*
- Up to 12 hours of smooth, sustained release
- Relative bioavailability equal to Quinidine Sulfate Tablets, USP
- Contains 48 mg more active quinidine than the leading gluconate product

*Some patients may require a t.i.d. dosage schedule.

For the proof, ask your Robins representative for a copy of the controlled crossover study. Or write S. Tisdale, M.D., 1211 Sherwood Avenue, Richmond, Va. 23220.

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5 ml
5 mg/5 ml
Lopressor®
metoprolol tartrate
For Intravenous Use
Dist. by:
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436-2620-A

Saving lives when the heart is under attack...

Intravenous Lopressor is now accepted as basic protocol for acute MI in more than 350 hospitals.

Reduces 3-month mortality[1]

Reduces incidence of ventricular fibrillation[2]

Reduces duration of chest pain and need for analgesics [1]

Lopressor®in MI

metoprolol tartrate

Ampuls: 5 mg/5 ml
Tablets: 50 mg
100 mg

Please see last page for Brief Summary of Prescribing Information.

436-2620-A

...and protecting healing hearts in the months ahead

The combination of early intravenous administration of Lopressor followed by long-term oral therapy resulted in a 36% reduction of three-month mortality in patients with definite or suspected acute MI in the Göteborg Trial.[1]

Treatment should be continued for 1-3 years.

Lopressor is contraindicated in patients with a heart rate <45 beats/min; significant heart block greater than first degree (P-R interval ≥0.24 sec); systolic blood pressure <100 mmHg; or moderate-to-severe cardiac failure. Please see last page for Brief Summary of Prescribing Information.

1. Hjalmarson Å, et al: The Göteborg Metoprolol Trial: Effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983 (June); 67(suppl 1):I-26-I-32.

2. Rydén L, et al: A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias. *N Engl J Med* 1983 (Mar 17); 614-617.

Lopressor® in **MI**

metoprolol tartrate

Ampuls: 5 mg/5 ml
Tablets: 50 mg
100 mg

Changing the Course of Cardiovascular Care

Saving lives when the heart is under attack

...and protecting healing hearts in the months ahead

Lopressor®
metoprolol tartrate **Tablets Ampuls**

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Myocardial Infarction
Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first-(P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent $beta_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a $beta_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and $beta_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness. Patients should contact the physician if any difficulty in breathing occurs, and before surgery of any type, the patient should inform the physician or dentist that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a 1-year study in dogs, there was no evidence of drug-induced toxicity at or below oral dosages of 105 mg/kg per day. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.
Pregnancy Category B
Reproduction studies have been performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg and have revealed no evidence of impaired fertility or teratogenicity due to Lopressor. Increased postimplantation loss and decreased neonatal survival did occur in the rats (threshold between 50 and 500 mg/kg), and distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

DOSAGE AND ADMINISTRATION
Myocardial Infarction
Early Treatment: During the early phase of definite or suspected acute myocardial infarction, treatment with Lopressor can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of Lopressor each; the injections should be given at approximately 2-minute intervals. During the intravenous administration of Lopressor, blood pressure, heart rate, and electrocardiogram should be carefully monitored.

In patients who tolerate the full intravenous dose (15 mg), Lopressor tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (see ***Late Treatment*** below).

Patients who appear not to tolerate the full intravenous dose should be started on either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with Lopressor should be discontinued (see **WARNINGS**).

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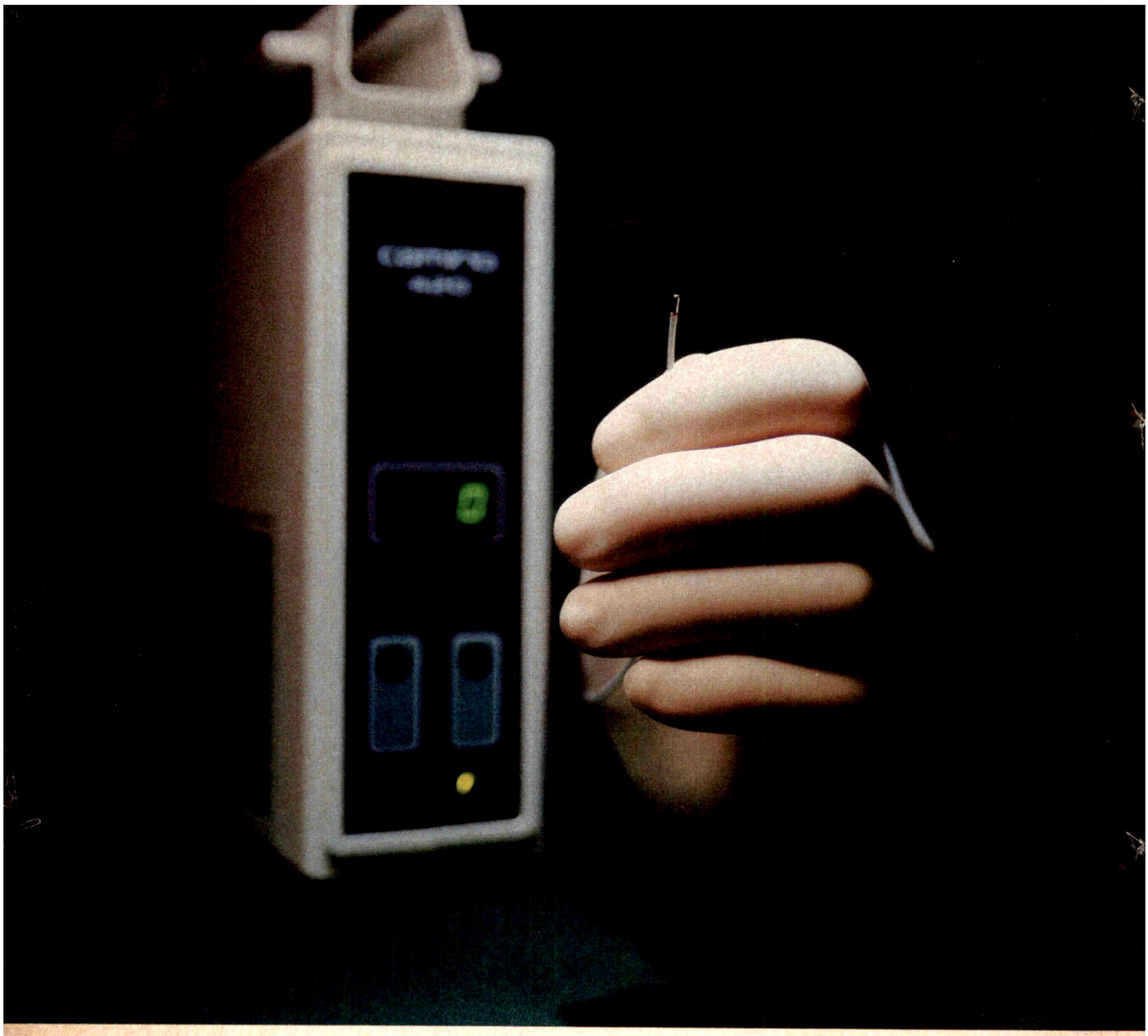

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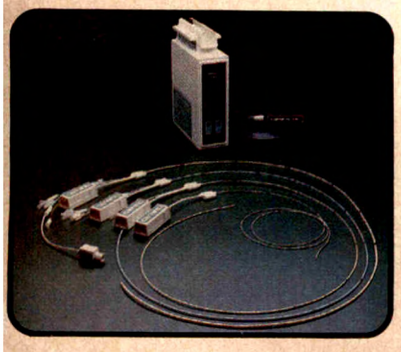

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Bruce M. Rothschild, MD

Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V.A. Medical Center North Chicago, Illinois

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REFERENCE 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

Please see preceding page for brief summary of prescribing information.

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CORONARY HEART DISEASE

Baseline Rest Electrocardiographic Abnormalities, Antihypertensive Treatment, and Mortality in the Multiple Risk Factor Intervention Trial

MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP

The overall results of the Multiple Risk Factor Intervention Trial (MRFIT) showed a nonsignificant 7% lower coronary artery disease (CAD) mortality rate in the special-intervention (SI) as compared to the usual-care (UC) group. The initial results also suggested that the SI program was more effective than UC in the community in reducing the CAD mortality rate in nonhypertensive persons than in hypertensive persons, and that the SI program used was more effective in reducing CAD deaths among men without than men with electrocardiographic (ECG) abnormalities at rest. Furthermore, an unfavorable mortality trend in hypertensive SI men with ECG abnormalities at rest compared with UC men was noted (adjusted relative risk of 1.67). Further analyses in baseline-defined subgroups indicated that (1) the most common ECG abnormalities at rest were high R waves and ST-T changes, (2) the CAD mortality differential (SI/UC) was similar in the subgroup with these abnormalities and in the subgroup with other abnormalities at rest, (3) the apparent excess CAD mortality among hypertensive SI men with ECG abnormalities at rest was manifested chiefly as sudden death within 1 hour, and (4) the association between ECG abnormalities at rest and the CAD mortality rate among hypertensive men was independent of the baseline level of blood pressure or of the findings on the exercise electrocardiogram. However, CAD mortality in those with abnormalities on the electrocardiogram both at rest and during exercise was lower in the SI than the UC group.

A possible explanation for the difference in outcome in the baseline-defined subgroup was an unexpectedly low UC mortality rate. However, within-group analysis revealed an interaction between ECG abnormalities at rest and diuretic treatment in the SI group, with the risk of CAD death for men prescribed diuretic drugs relative to men not prescribed diuretic drugs estimated as 3.34 among men with baseline ECG abnormalities at rest and as 0.95 among men without such abnormalities. No such effect was found in the UC group, in which men generally were prescribed lower doses of hydrochlorothiazide and chlorthalidone than SI men. However, analyses do not suggest an effect of diuretic dose or of hypokalemia on the CAD mortality rate in treated SI participants. Although subgroup analyses must be interpreted with caution, particularly those that go beyond the randomized clinical trial design by the MRFIT, these findings pose hypotheses for investigation by other researchers in systemic hypertension and may have implications for therapy. **(Am J Cardiol 1985;55:1–15)**

The participating investigators and their institutional affiliations are listed in the Appendix. Manuscript received June 15, 1984; revised manuscript received September 10, 1984, accepted September 11, 1984.

Address for reprints: Marcus O. Kjelsberg, PhD, Biometry Division, School of Public Health, University of Minnesota, Suite 508, 2829 University Avenue Southeast, Minneapolis, Minnesota 55414.

The Multiple Risk Factor Intervention Trial (MRFIT) was a randomized primary prevention trial that tested the effect of a multifactor intervention program on mortality from coronary artery disease (CAD) in 12,866 men aged 35 to 57 years, selected on the basis of elevated

serum cholesterol level, or high diastolic blood pressure (BP), or cigarette smoking, or a combination of these factors. The previously reported mortality results of the MRFIT showed a nonsignificant 7% lower CAD mortality rate in the special-intervention (SI) compared with the usual-care (UC) group.[1] An explanation for these findings—that risk factor reduction is simply ineffective—was noted as unlikely in the initial report, given the weight of findings from other studies. Two other explanations are plausible.

First, the CAD and total death rates were considerably lower than had been anticipated in both SI and UC participants. This reduced the power to test the principal hypothesis; thus, the confidence interval about the CAD mortality difference ranged from 25% benefit to 15% harm (approximate 90% limits). The inconclusive result may therefore represent a type II error—a false-negative finding due to chance. The second plausible explanation was that the mortality comparison between all SI and UC participants represented an average of differential responses in important subgroups. For example, there were 35 SI and 45 UC deaths from CAD among men who were not hypertensive at baseline, whereas there were 80 SI and 79 UC CAD deaths among those who were hypertensive.[1] Within the hypertensive subgroup, SI death rates from CAD and all causes were lower than UC death rates for men free of baseline electrocardiographic (ECG) abnormalities at rest. However, hypertensive SI participants with baseline ECG abnormalities at rest had more CAD deaths than their UC counterparts. Furthermore, and in contrast, SI participants with ECG abnormalities during exercise at entry had a significant 57% lower CAD mortality rate than the similar group of UC participants.[2] These findings support the interpretation that the MRFIT total experience represents the sum of substantially different findings in various subgroups.

In this article the CAD mortality findings for nonhypertensive and hypertensive men with and without ECG abnormalities at rest are examined further. In addition, the association between diuretic use and CAD mortality is studied and possible mechanisms are considered.

Design and Methods

Design: The design of the MRFIT has been described.[1,3,4] Briefly, male volunteers, mostly from employee groups, were recruited in 18 U.S. cities. They were screened to select those in the upper 15% (later changed to 10%) of a risk-score distribution derived from Framingham data, with the score a function of serum cholesterol concentration, cigarette smoking and diastolic BP. Those free of overt CAD by history and electrocardiogram at rest otherwise suitable for a long-term trial, and agreeable to being randomized, were assigned in essentially equal numbers to SI and UC groups. SI men participated in an intensive program aimed at lowering blood cholesterol levels by nutritional means, eliminating cigarette smoking through education and behavior modification techniques, and reducing diastolic BP of hypertensive men primarily using a stepped-care drug regimen. UC participants were referred to their customary source of medical care along with information on risk factor status, but were given no advice as to intervention. Both groups were examined annually over 6 to 8 years for determination of risk factors and morbid endpoints. CAD mortality was the primary endpoint; ascertainment of vital status at the end of follow-up in February 1982 was 99.7% complete, and a cause of death was assigned in all but 3% of deaths.[1]

Before termination of the trial and access to endpoint data, the MRFIT Steering Committee formulated 2 subgroup hypotheses related to baseline ECG abnormalities at rest and to ECG response to a heart-rate-limited exercise test, respectively. One postulated that among men without baseline ECG abnormalities at rest, the SI group would have a lower CAD mortality than the UC group. Similarly, the other postulated a corresponding difference in participants with a normal electrocardiogram during exercise. It was presumed that men in each subgroup had less advanced cardiac involvement and therefore would be more responsive to the intervention effort than men who had ECG abnormalities. Because men without ECG abnormalities made up the great majority of the MRFIT cohort, there was judged to be reasonable power to test these postulates. Neither hypothesis incorporated any relation to hypertension or antihypertensive treatment. However, prior analysis plans called for assessing endpoint data for specific subgroups, e.g., those hypertensive at baseline, to determine whether MRFIT findings were consistent with those of the Hypertension Detection and Follow-up Program.[5] The number of men with hypertension at baseline was not, however, large enough to warrant formulating a specific and formal hypothesis.

Baseline and follow-up measurements: BP was measured on 3 occasions before randomization. At initial screening, BP was measured 3 times to determine, along with number of cigarettes smoked per day and total serum cholesterol, if the man met risk eligibility criteria. Four additional BP measurements with the man seated after a 5-minute rest were made at both second and third screening visits. Baseline BP was defined as the average of the 2 random-0 manometer readings at second screening and the 2 random-0 readings at third screening. A participant was considered hypertensive at entry if his baseline diastolic BP was 90 mm Hg or higher, or if he reported that he was currently taking antihypertensive drugs at the second screening. Follow-up diastolic BP recorded at annual visits was similarly measured and defined (average of 2 random-0 readings).

Electrocardiograms at rest were performed at the second screening and read at the local clinics to exclude from the study men with evidence of a previous myocardial infarction, major atrioventricular conduction defect, complete bundle branch block, or arrhythmia that required treatment.* Another electrocardiogram at rest was recorded at third screening, and was read according to the Minnesota code[6] both visually at the ECG Coding Center (University of Minnesota) and by computer algorithm at the Computer ECG Center (Dalhousie University).*

Because of the performance of an exercise test at the third screening, modified limb electrode positions were used to record the standard 12-lead electrocardiogram at this visit. The modified lead placements have been described.[2] Because of the torso placement of the limb electrodes, R-wave abnormalities were coded at baseline using chest leads only.[7†]

* Resting ECG exclusion criteria (Minnesota codes) were as follows: at second screening, 1.1, 1.2 plus 5.1 or 5.2, 6.1, 6.2, 6.2.2, 6.4, 7.1.1, 7.2.1, 7.4 plus 5.1 or 5.2, 8.2.2, 8.3, any paroxysmal tachyarrhythmia; at third screening, 1.1, 1.2 plus 5.1 or 5.2.

† An exception to this coding rule was made for 1 clinical center where the electrocardiograms initially produced a false calibration. When the recalibrated tracings were read during the middle of the trial, R-wave abnormalities were coded using both chest and modified limb leads.

Since the computer identified approximately 34% more participants with ECG abnormalities at rest than did the visual coding, key analyses were performed based on both the computer and visually determined Minnesota codes. The associations identified using the visually coded data were not substantially altered by use of the computer coding. The data from electrocardiograms at rest presented in this report were derived from the visual readings only, for consistency with the earlier report on mortality findings.[1]

An electrocardiogram during exercise was also performed at the third screening, and its detailed findings are the subject of a separate paper.[2] Briefly, participants exercised on a treadmill with stepwise increase of slope and speed until a predetermined heart rate was reached, or to an earlier termination for specified reasons. An abnormal exercise test was defined based on the computer classification of ST-segment depression, measured as the area between this segment and the isoelectric line. The criteria were as follows: an ST-depression integral of at least 16 μV-s at peak exercise or in the immediate or 3-minute recovery record in any of the leads CS_5, aVL, aVF or V_5, with the ST-depression integral in the preexercise sitting record less than 6 μV-s in all of these leads.

Blood chemistry determinations at screening and annual visits included serum or plasma levels of cholesterol, triglycerides, lipoproteins, thiocyanate, and potassium, and were performed using methods previously described.[8,9]

Intervention on blood pressure: A goal BP was established if an SI participant reported having antihypertensive medication prescribed for him by his personal physician (regardless of BP level), or if an untreated man was found to have a diastolic BP of 90 mm Hg or higher on 2 consecutive monthly visits, beginning with and including the third screening visit. The reading at the second of these visits was used to establish the treatment goal: either 89 mm Hg or a reduction of 10 mm Hg, whichever was lower, but not less than 80 mm Hg. Men who had a diastolic BP of 90 mm Hg or less and who were already taking antihypertensive drugs prescribed by a personal physician were assigned a goal of 80 mm Hg. Before drug prescription, weight reduction was attempted for overweight men. Drugs were prescribed according to a stepped-care protocol beginning with 50 mg of either hydrochlorothiazide or chlorthalidone, at the discretion of the clinic physician, up to a maximal dose of 100 mg/day.

In 1979, during the fourth to fifth year of follow-up, data suggesting an adverse response to the BP intervention were noted by the Coordinating Center and reported to the Policy Advisory Board. Based on these findings, and in light of the then recently reported successful outcome of the Hypertension Detection and Follow-up Program, in which chlorthalidone has been used as the main diuretic drug,[5] it was decided that all clinics should change therapy from hydrochlorothiazide to chlorthalidone as the diuretic of choice. Because it had become widely recognized that a smaller dose of diuretic usually resulted in BP lowering similar to that of a larger dose,[10] clinics were advised to switch SI participants prescribed hydrochlorothiazide to 50 mg of chlorthalidone irrespective of the currently prescribed dosage of hydrochlorothiazide. These changes in the protocol were largely implemented between March and June, 1980. The data related to this change will be described in greater detail in another report.

Further details of the MRFIT stepped-care protocol, including step II, III and IV drugs, have been published.[1,11] SI men were seen at least every 4 months; those assigned a goal BP were seen more often until goal was reached. Serum levels of potassium were determined and reported centrally every 4 months.

The decisions on when and how to treat UC participants for hypertension were made by their own physicians. These men were seen yearly at MRFIT clinics, at which time they were questioned about current medications and requested to bring these to the examination. Their personal physicians received reports, including BP measurements, of each annual MRFIT examination.

Determination of endpoints: Methods of mortality ascertainment have been reported.[1] Classification of cause of death was performed by a committee of 3 cardiologists not affiliated with MRFIT in any other respect. They used hospital records, physicians' reports, next-of-kin interviews, death certificates and autopsy reports (in about one-third of deaths in each group). Group assignment was carefully masked. CAD deaths were subclassified as (1) documented myocardial infarction; (2) sudden death within 60 minutes, or between 1 and 24 hours of symptom onset, without documented myocardial infarction; (3) congestive heart failure due to CAD; or (4) death associated with surgery for CAD.

Statistical methods: Mortality results are presented in life-table functions using the Kaplan-Meier product limit method.[12] Comparisons of mortality for baseline defined subgroups were summarized using the log-rank test.[13] Heterogeneity of relative risks (SI/UC) for baseline defined subgroups was evaluated using the Cox proportional hazards model[14] with Breslow's approximation.[15] Interaction terms were defined that involved an indicator variable for study group (SI or UC) and the other factor under study, e.g., the presence or absence of ECG abnormalities at rest or baseline hypertensive status. The significance of the interaction with study group was evaluated by considering the maximized log likelihood for the model with and without the interaction term.

A test for the linear trend of relative risk estimates was performed using weighted least squares. The log odds ratio for each stratum was regressed on the midpoint of the stratum. Weights were chosen as the inverse of the variance of the log odds ratio.

Univariate comparisons of the relation to mortality of variables related to treatment of hypertension were made using person-years analyses. In these analyses length of exposure in days to the factor under study, e.g., treatment status (no diuretic, diuretic), was tabulated and summed across individual participants and periods of follow-up. The exposure period was approximated using data on current status reported at annual visits.

The Cox proportional hazards model adapted for use with time-dependent covariates was used to investigate the association of characteristics of the hypertension intervention program and subsequent CAD death. In these analyses covariates for age, the initial levels of diastolic BP, serum cholesterol and cigarette smoking, change in serum cholesterol, change in diastolic BP (in some models), and an indicator variable for thiocyanate-confirmed smoking cessation were included in the regression model, as well as indicator variables to denote diuretic prescription, the presence or absence of ECG abnormalities at rest, and the interaction of ECG abnormalities at rest with diuretic use. The characteristics under study were updated annually through 7 years, and missing observations were assigned the value from the last attended annual follow-up visit. The statistical significance of the regression coefficient corresponding to the interaction of diuretic use and baseline ECG abnormalities at rest was determined by examining the increase in the maximized log likelihood compared with the model that did not allow for an interaction.

MRFIT was not designed to estimate effects of individual intervention, i.e., a factorial arrangement of the intervention was not used. Therefore, much of this investigation involved the use of a statistical model to adjust for possible influences of various risk factors on outcome. For example, unadjusted SI-UC comparisons of hypertensive and nonhypertensive

TABLE I Risk Factor Change and Antihypertensive Drug Use at 48 Months for Men in the Special-Intervention and Usual-Care Groups According to the Presence of Baseline Electrocardiographic Abnormalities at Rest

	Rest ECG Abnormalities Absent			Rest ECG Abnormalities Present		
	SI	UC	SI-UC	SI	UC	SI-UC
Serum cholesterol change (mg/dl)	−19.2	−10.7	−8.5	−17.2	−9.1	−8.1
LDL cholesterol change (mg/dl)	−11.6	−5.8	−5.8	−12.2	−6.7	−5.5
HDL cholesterol change (mg/dl)	0.7	0.9	−0.2	0.5	0.6	−0.1
Triglyceride change (mg/dl)	−7.7	−2.6	−5.1	−2.0	6.1	−8.1
Weight change (lbs)	−3.3	0.1	−3.4	−3.2	−0.6	−2.6
Quit smoking rate thiocyanate adjusted	31.5	19.2	12.3	32.6	19.8	12.8
Change in diastolic BP (mm Hg)	−8.7	−4.7	−4.0	−10.2	−5.7	−4.5
% prescribed antihypertensive drugs	54.6	38.5	16.1	61.5	46.7	14.8
% prescribed ≤50 mg chlorthalidone	8.2	3.2	5.0	10.6	3.2	7.4
% prescribed >50 mg chlorthalidone	10.9	1.0	9.9	9.9	1.7	8.2
% prescribed ≤50 mg hydrochlorothiazide	15.6	20.4	−4.8	17.8	24.2	−6.4
% prescribed >50 mg hydrochlorothiazide	14.4	2.9	11.5	17.5	3.8	13.7
% prescribed reserpine	14.6	5.5	9.1	17.8	5.9	11.9
% prescribed methyldopa	5.9	7.0	−1.1	7.5	8.9	−1.4
% prescribed propranolol	11.9	6.0	5.9	12.4	6.6	5.8
% prescribed hydralazine	7.3	3.4	3.9	9.1	4.7	4.4
% prescribed KCl	11.6	3.5	8.1	14.2	5.2	9.0
% prescribed spironolactone or triamterene	4.7	8.5	−3.8	5.0	10.5	−5.5
Serum potassium change (mEq/liter)	−0.3	−0.1	−0.2	−0.3	−0.1	−0.2

BP = blood pressure; HDL = high-density lipoprotein; KCl = potassium chloride; LDL = low-density lipoprotein; MRFIT = Multiple Risk Factor Intervention Trial; SI = special intervention; UC = usual care.

subjects at entry implicitly assume that the degrees of smoking and dietary intervention were similar for SI hypertensive and nonhypertensive subjects. This was unlikely, since the trial selection criteria resulted in higher serum cholesterol levels and more cigarette smoking for nonhypertensive men than hypertensive men at entry and, consequently, possible differential intervention in these areas during follow-up. Multivariate analyses were used to attempt to control for these differences, but results of such analyses can be influenced by the particular set of covariates used. By definition, comparisons of baseline-defined subgroups do not take into account the actual interventions used and risk factor changes achieved. To go beyond this limitation, within-group analyses of subgroups defined by factors determined after randomization were performed. For such within-group analyses, inferences are limited, because of the lack of a randomized control group.

Significance probabilities (p values) are unadjusted for multiple comparisons and thus those cited should be viewed only as guidelines. In accordance with usual standards, 2-sided p values <0.05 are termed nominally significant.

Results

Coronary artery disease mortality rate in baseline-defined subgroups (special-intervention vs usual-care): As of February 28, 1982, after an average period of follow-up of 7 years, there were 88 CAD deaths among UC men (18.8 per 1,000) without ECG abnormalities at rest and 68 CAD deaths among SI men (14.8 per 1,000) without ECG abnormalities at rest. The life table Z value of −1.54 (p = 0.12) for men without ECG abnormalities at rest gives some support to the hypothesis that the SI men would have a lower CAD mortality rate than the UC group in this subgroup, but the observed difference could also well be due to chance. For men with ECG abnormalities at rest, SI participants had a higher CAD mortality rate than UC men (47 SI CAD deaths compared to 36 UC deaths), but again the difference is not statistically significant (Z = 1.09, p = 0.28). The difference in the relative risk of CAD death (SI/UC) for men with (1.26) and without (0.79) ECG abnormalities at rest is large but nonsignificant (nominal p = 0.08). This difference suggests some heterogeneity of outcome and attenuation of benefit of risk factor intervention for men with ECG abnormalities at rest.

Because the intervention itself could have differed according to ECG findings at baseline, risk factor levels and use of antihypertensive treatment at 48 months, a point somewhat more than halfway through the study, are compared for SI and UC men with and without ECG abnormalities at rest (Table I). The SI-UC differences in risk factor levels and in the use of antihypertensive drugs are similar for the 2 subgroups defined by the presence/absence of baseline ECG abnormalities at rest. Therefore, it seems unlikely that the apparent difference noted in relative risk (SI/UC) of CAD death for men with and without ECG abnormalities at rest arises from differential degrees of intervention, relative to UC changes, for the 2 subgroups.

This apparent difference in relative risks was investigated further to determine whether any components of the intervention were associated with a decreased benefit. Initial evidence[1] indicated that the differential effectiveness of the intervention according to the presence of baseline ECG abnormalities at rest was associated with baseline hypertensive status. This finding is illustrated by adjusted relative risk (SI/UC) estimates for dichotomized levels of the risk factors at baseline (Table II). For men without ECG abnormalities at rest, no substantial differences were noted in the relative risk estimates by level of the risk factors. In the presence of ECG abnormalities at rest, there were also only minimal differences for strata defined by smoking status and level of serum cholesterol. However, the difference in relative risks between hypertensive and nonhypertensive subgroups are larger and on opposite sides of

TABLE II **Adjusted* Relative Risk (Special Intervention/Usual Care) of Coronary Artery Disease Death for Multiple Risk Factor Intervention Trial Participants by Each Baseline Risk Factor and Presence of Baseline Electrocardiographic Abnormalities at Rest**

	Baseline Rest ECG Abnormalities			
	Absent		Present	
Risk Factor Subgroups	Relative Risk (SI/UC)	p Value for Difference in Relative Risk	Relative Risk (SI/UC)	p Value for Difference in Relative Risk
Nonsmokers	0.63	0.42	1.39	0.81
Smokers	0.84		1.23	
Serum cholesterol <250 mg/dl	0.92	0.33	1.04	0.50
Serum cholesterol ≥250 mg/dl	0.67		1.42	
Nonhypertensive	0.82	0.82	0.71	0.08
Hypertensive	0.76		1.67	

* Adjusted for the other 2 risk factors by Cox proportional hazards regression.
SI = special intervention; UC = usual care.

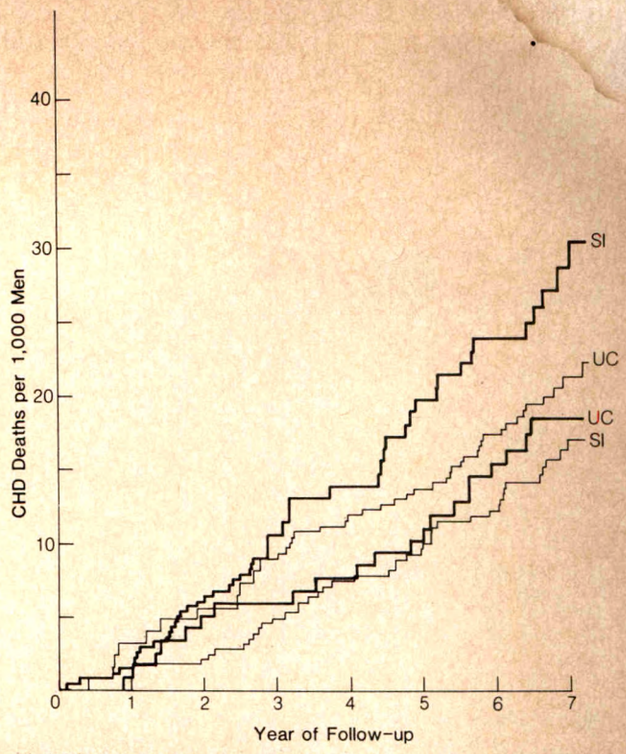

FIGURE 1. Cumulative coronary heart disease (CHD) mortality rates for hypertensive men in the special-intervention (SI) and usual-care (UC) groups according to the presence or absence of electrocardiographic (ECG) abnormalities at rest. The **heavy line** indicates men with baseline ECG abnormalities at rest and the **thin line** indicates men without ECG abnormalities at rest.

unity, although not nominally significant (p = 0.08 by Cox regression). This finding suggests that the higher relative risk (SI/UC) among men with ECG abnormalities at rest is concentrated among those who were hypertensive at baseline. Therefore, the CAD mortality rate for hypertensive men only, with and without ECG abnormalities, was compared for SI and UC men (Fig. 1). In hypertensive participants with ECG abnormalities, the cumulative mortality curves for the SI and UC groups were not significantly different (p = 0.06 by log-rank test). However, the estimated difference in the relative risks of CAD death (SI/UC) for hypertensive men with (1.67) and without (0.76) ECG abnormalities at rest is nominally significant (p = 0.02) by Cox regression.

The distribution of ECG abnormalities by main categories of the Minnesota code is shown in Table III. High R waves occurred in 39% of those with abnormalities, almost exclusively with a left-sided pattern (M.C.3.1, 3.3). Other categories found in at least 10% of those with ECG abnormalities were intraventricular conduction defects, negative T waves, arrhythmias and left-axis deviation. The percentage of participants with high R waves was directly related to diastolic BP at

TABLE III **Frequency Distribution of Baseline Electrocardiographic Abnormalities at Rest and Mean Baseline Diastolic Blood Pressure for Multiple Risk Factor Intervention Trial Participants in Both Special-Intervention and Usual-Care Groups***

Type of Abnormality (MC)	No. of Participants	% of All Participants	% of Those with Abnormalities	Baseline Diastolic BP (mm Hg)
High R waves (3.1–3.3)	1,410	11.0	39.2	93.5
IV conduction defects (7.1–7.8)	869	6.8	24.1	90.1
Negative T waves (5.1–5.3)	511	4.0	14.2	94.7
Arrhythmias (8.1–8.6)	490	3.8	13.6	91.5
Left-axis deviation < −30°	380	3.0	10.6	92.6
ST elevation (9.2)	240	1.9	6.7	90.4
ST depression (4.1–4.3)	236	1.8	6.6	95.1
Q–QS waves (1.1–1.3)	184	1.4	5.1	92.3
AV conduction defects (6.1–6.8)	180	1.4	5.0	89.8
Right-axis deviation ≥ 120°	17	0.1	0.5	91.4
Low QRS amplitude (9.1)	6	0.0	0.2	85.7
Any abnormality	3,593	27.9	100.0	92.0
No abnormality	9,272	72.1	. . .	90.5

* The abnormalities are not mutually exclusive and therefore participants may be counted more than once.
AV = atrioventricular; BP = blood pressure; IV = intraventricular; MC = Minnesota code.

TABLE IV Number of Coronary Artery Disease Deaths (per 1,000) and Relative Risk (Special Intervention/Usual Care) for Multiple Risk Factor Intervention Trial Participants by Hypertensive Status at Baseline and Presence of Baseline Electrocardiographic Abnormalities at Rest

	No. of Participants		CAD Deaths		
	SI	UC	SI	UC	SI/UC
Nonhypertensive					
ECG abnormalities at rest					
Absent	1,817	1,862	24 (13.2)	30 (16.1)	0.82
Present	592	583	11 (18.6)	15 (25.7)	0.72
High R waves and/or negative T waves*	223	207	5 (22.4)	7 (33.8)	0.66
Other abnormalities	369	376	6 (16.3)	8 (21.3)	0.77
Total	2,409	2,445	35 (14.5)	45 (18.4)	0.79
Hypertensive					
ECG Abnormalities at rest					
Absent	2,785	2,808	44 (15.8)	58 (20.7)	0.76
Present	1,233	1,185	36 (29.2)	21 (17.7)	1.65
High R waves and/or negative T waves*	698	688	26 (37.2)	15 (21.8)	1.71
Other abnormalities	535	497	10 (18.7)	6 (12.1)	1.55
Total	4,018	3,993	80 (19.9)	79 (19.8)	1.00

* Minnesota code (MC) 3.1-3.3 and/or 5.1-5.3; ST depression—MC 4.1-4.3—is included in T-wave abnormalities, since coding rules require a code for negative T wave whenever ST depression is present. Only 31 tracings met the combined R and ST-T criteria for definite left ventricular hypertrophy: MC 3.1 + 4.1-4.3 or 5.1-5.3.

CAD = coronary artery disease; SI = special intervention; UC = usual care.

TABLE V Number of Coronary Artery Disease Deaths (per 1,000) and Relative Risk (Special Intervention/Usual Care) for Multiple Risk Factor Intervention Trial Participants by Hypertensive Status at Baseline and the Presence of Baseline Electrocardiographic Abnormalities at Rest

	Rest ECG Abnormalities					
	Absent			Present		
	SI	UC	SI/UC	SI	UC	SI/UC
Nonhypertensive	24 (13.2)	30 (16.1)	0.82	11 (18.5)	15 (25.7)	0.72
Hypertensive	44 (15.8)	58 (20.7)	0.76	36 (29.2)	21 (17.7)	1.65
On medication at S_2	16 (18.8)	18 (22.0)	0.85	12 (29.3)	8 (19.5)	1.50
Not on medication at S_2						
90–94	11 (13.2)	9 (10.4)	1.27	6 (18.7)	3 (9.5)	1.97
95–99	10 (16.9)	17 (27.2)	0.62	9 (38.0)	2 (9.0)	4.22
≥100	7 (13.9)	14 (27.9)	0.50	9 (33.8)	8 (33.8)	1.00
Total	68 (14.8)	88 (18.8)	0.79	47 (25.7)	36 (20.4)	1.26

S_2 = second screening visit; SI = special intervention; UC = usual care.

baseline, as was the percentage with negative T waves and the percentage with ST depression ($p < 0.01$ for linear trend for each); other abnormalities were not associated with baseline BP.

Accordingly, SI-UC mortality was compared separately in those with R or ST-T-wave abnormalities and in those with other abnormalities (Table IV). The 65% higher CAD mortality rate (relative risk of 1.65, similar to the adjusted relative risk of 1.67 in Table II) among hypertensive men in the SI group with ECG abnormalities at rest compared with those in the UC group contrasts with lower SI than UC rates in hypertensive men without abnormalities and in nonhypertensive participants. The estimated relative risk (SI/UC) for hypertensive men is larger, but not significantly so, in those men with R- or T-wave changes (1.71) compared with men with other ECG abnormalities (1.55), both being larger than the relative risk in hypertensive men with no ECG abnormalities at rest (0.76). UC hypertensive men with ECG abnormalities at rest had a lower CAD mortality rate (17.7 per 1,000) than those without abnormalities (20.7 per 1,000), in contrast with the parallel comparison in UC nonhypertensive men (25.7 vs 16.1 per 1,000).

In the earlier report,[1] the relative risk of CAD death and death from any cause (SI/UC) was noted to increase with decreasing baseline diastolic BP among hypertensives, with an indication of a possible adverse effect in the SI group among those with entry levels of 90 to 94 mm Hg. The test for linear trend of relative risk estimates (SI/UC) yielded a nominal p value of 0.11 for CAD death and 0.001 for death from any cause. The cross-classification of SI and UC by level of baseline diastolic BP and ECG abnormalities at rest is given in Table V. At each level of baseline diastolic BP among hypertensive men, the relative risk (SI/UC) estimate for men with ECG abnormalities is larger than that for men without ECG abnormalities. Also, among men without as well as men with ECG abnormalities at rest, the relative risk (SI/UC) of CAD death is lower at the higher levels of baseline diastolic BP, with an estimate of 1.0 at a BP of 100 mm Hg or higher in those with abnor-

TABLE VI Number of Deaths by Cause for Multiple Risk Factor Intervention Trial Participants Who Were Hypertensive at Baseline, by Presence of Baseline Electrocardiographic Abnormalities at Rest

	Baseline Rest ECG Abnormalities							
	Absent				Present			
	SI		UC		SI		UC	
Cause of Death	No. of Deaths*	No. of 1,000	No. of Deaths	No. of 1,000	No. of Deaths*	No. of 1,000	No. of Deaths	No. of 1,000
CAD	44	15.8	58	20.7	36	29.2	21	17.7
Myocardial infarction	15	5.4	14	5.0	9	7.3	8	6.8
Sudden death within 60 min	19	6.8	23	8.2	21	17.0	8	6.8
Sudden death 60 min–24 hr	9	3.2	16	5.7	4	3.2	5	4.2
Other	1	0.3	5	1.8	2	1.6	0	0.0
Other cardiovascular	9	3.2	12	4.3	9	7.3	4	3.4
Stroke	7	2.5	7	2.5	4	3.2	2	1.7
Other	2	0.7	5	1.8	5	4.1	2	1.7
Noncardiovascular	45	16.1	49	17.5	25	20.3	22	18.5
Unknown	2	0.7	3	1.1	4	3.2	0	0.0
Total	100	35.9	122	43.4	74	60.0	47	39.7

* As of February 28, 1982.
CAD = coronary artery disease; SI = special intervention; UC = usual care.

TABLE VII Number and Rate (per 1,000) of Coronary Artery Disease Deaths for Multiple Risk Factor Intervention Trial Participants by Hypertensive Status at Baseline and According to the Presence of Electrocardiographic Abnormalities at Rest and During Exercise*

Baseline Rest ECG Abnormalities (Visual)	Baseline Exercise ECG Abnormalities (Computer)	Nonhypertensive		Hypertensive		Total	
		SI	UC	SI	UC	SI	UC
Absent	Absent	22 (14.0)	19 (11.9)	35 (15.1)	40 (17.0)	57 (14.6)	59 (14.9)
Present	Absent	7 (14.8)	7 (15.0)	20 (22.8)	7 (8.2)	27 (20.0)	14 (10.6)
Absent	Present	2 (10.8)	8 (46.5)	5 (16.1)	13 (43.2)	7 (14.1)	21 (44.4)
Present	Present	3 (40.0)	7 (79.5)	7 (36.3)	10 (57.8)	10 (37.3)	17 (65.1)

* Excluded from this table are 135 SI and 142 UC men with ischemia during rest, among whom there were 5 SI and 2 UC CAD deaths, and 284 SI and 288 UC men who did not participate in the exercise test, among whom there were 9 SI and 11 UC CAD deaths.
CAD = coronary artery disease; SI = special intervention; UC = usual care.

malities. Although the apparent increased risk of SI men at the lower diastolic BP levels compared with UC does not appear to be explained by the findings regarding the ECG abnormalities at rest, the numbers of deaths at each level of diastolic BP are small.

An expanded comparison of cause-specific mortality for hypertensive participants is shown in Table VI, by presence or absence of ECG abnormalities at rest. The greater number of SI than UC CAD deaths in the presence of ECG abnormalities at rest was concentrated among sudden deaths occurring within 1 hour (life-table Z value for SI vs UC hypertensive men with ECG abnormalities at rest of 2.34, nominal $p = 0.02$). In hypertensive men with ECG abnormalities there were no SI-UC differences in numbers of deaths from myocardial infarction or in sudden death from 1 to 24 hours. The numerical difference in total mortality in this subgroup (74 SI vs 47 UC deaths) is nominally significant ($p = 0.02$), and is twice as great as for CAD deaths alone, resulting from a few more SI than UC deaths in each category of non-CAD death (other cardiovascular disease, noncardiovascular disease, and unknown cause). In the absence of ECG abnormalities there were fewer SI than UC deaths (life-table $Z = -1.49$, $p = 0.14$), mainly from cardiovascular disease, but with no apparent difference in deaths from myocardial infarction or stroke.

The increased relative risk (SI/UC) for hypertensive participants with ECG abnormalities at rest compared with similar men without ECG abnormalities at rest and to normotensive men has also been examined with stratification based on presence of ECG abnormalities during exercise. Among men who participated in the exercise ECG (95.6% of all randomized men), the percent of participants with an abnormal ECG during or immediately after the exercise test, using the computer criteria (see Design and Methods section), was 12.2%. A positive response was strongly related to risk of CAD death in the UC group (Table VII). Comparison of SI-UC differences revealed that when baseline ECGs both at rest and during exercise were abnormal, for both hypertensive and normotensive participants, SI rates were considerably lower than UC rates (row 4, Table VII). The SI-UC differences were larger when the exercise ECG was abnormal and the electrocardiogram at rest was normal (row 3). When the electrocardiogram during exercise was normal and the electrocardiogram at rest was abnormal, the CAD mortality rate of hypertensive men in the UC group was unexpectedly low, only 8.2/1,000/7 years, and the SI rate was much higher

TABLE VIII Number and Rate (per 1,000 person-years) of Coronary Artery Disease Deaths for Multiple Risk Factor Intervention Trial Participants in the Special-Intervention Group by Hypertensive Status at Baseline, by the Presence of Baseline Electrocardiographic Abnormalities at Rest and by Diuretic Therapy at Last Annual Visit

	Baseline Rest ECG Abnormalities					
	Present			Absent		
Hypertension and Treatment Status	Person-years	No. of Deaths	Per 1,000 pers.-yrs.	Person-years	No. of Deaths	Per 1,000 pers.-yrs.
Hypertensive at baseline						
On diuretic	5,737	34	5.93	12,376	28	2.26
Not on diuretic	2,637	2	0.76	6,772	16	2.36
Total	8,374	36	4.30	19,148	44	2.30
Nonhypertensive at baseline						
On diuretic	696	4	5.75	2,023	5	2.47
Not on diuretic	3,437	7	2.04	10,584	19	1.80
Total	4,133	11	2.66	12,607	24	1.90
All						
On diuretic	6,433	38	5.91	14,399	33	2.29
Not on diuretic	6,074	9	1.48	17,356	35	2.02
Total	12,507	47	3.76	31,755	68	2.14

The relative risk (diuretic/no diuretic) in the presence of ECG abnormalities at rest is 3.99 (5.91/1.48); the corresponding relative risk in the absence of ECG abnormalities at rest is 1.13 (2.29/2.02).

than the UC rate (row 2). Among nonhypertensive men in this subgroup, as well as in hypertensive and nonhypertensive men with neither rest nor exercise ECG abnormalities (row 1), CAD mortality rates were similar with only small SI-UC differences.

Overall statistical comparison of the joint effect of ECG findings at rest and during exercise suggests that these were independent influences on the differences in CAD mortality between the SI and UC groups ($p = 0.96$ for test of hypothesis of dependence, for hypertensive and nonhypertensive men combined). Specifically, for the total group, among men with a normal ECG during exercise, the relative risk (SI/UC) of CAD death was 0.98 (14.6/14.9) for men with a normal ECG response at rest and 1.89 (20.0/10.6) for men with an abnormal ECG response at rest, the latter relative risk being approximately twice as large as the former. For men with an abnormal ECG response during exercise, the corresponding relative risk estimates were 0.32 and 0.57. Again, the relative risk (SI/UC) for men with ECG abnormalities at rest was approximately twice as large as the corresponding estimate for men with a normal ECG response at rest. However, as noted above, a net adverse effect was apparent only for hypertensive SI men with a normal exercise test response and an abnormal ECG at rest.

Coronary artery disease mortality in subgroups defined after randomization—antihypertensive treatment: The findings in subgroups defined by baseline characteristics pose a possible problem with the hypertension intervention program for men with baseline ECG abnormalities at rest. Since drug treatment was the primary means of lowering BP for SI participants, the question was examined as to whether some aspect of the pharmacologic treatment or some consequence thereof, was associated with an increased CAD risk for men with ECG abnormalities at rest. To do so, within-group analyses based on factors occurring postrandomization had to be used; these do not preserve the randomized design of the trial and are more subject to bias by confounding variables.

As previously reported,[1,11] drug therapy was widely used in both SI and UC groups, with 58% of SI and 47% of UC participants prescribed medication by the 6-year follow-up. Even in participants with baseline diastolic BP less than 90 mm Hg, there was a gradual increase in the use of medication during follow-up as participants with borderline levels reached the criterion for hypertension. The prevalence of drug treatment in such men was 26% in the SI and 18% in the UC group at the sixth annual visit. In both SI and UC groups, treatment was slightly more frequent in those with than in those without ECG abnormalities (Table I). Those with abnormalities also had a mean baseline diastolic BP 1.5 mm Hg higher than those without (Table III).

Because of different patterns of use of specific diuretics, including dosage, in the SI and UC groups, relations of treatment variables with ECG abnormalities and CAD mortality are discussed separately. The data for SI participants were subdivided by presence of hypertension at baseline (Table VIII) as a means of controlling for entry level BP differences between men subsequently prescribed and those not prescribed a diuretic drug. In both of the strata SI men with baseline ECG abnormalities had a higher CAD mortality rate if they were receiving diuretic drugs at their most recent annual examination than if they were not (5.93 vs 0.76 and 5.75 vs 2.04 per 1,000 person-years, for hypertensive and nonhypertensive subgroups, respectively). No such differences were seen in the absence of ECG abnormalities, the CAD rates exhibiting remarkable similarity for those taking and those not taking diuretic drugs.

SI participants not prescribed diuretic drugs do not represent an ideal comparison group for those receiving these drugs even among hypertensive participants. A few not taking diuretic drugs were prescribed other antihypertensive medications. Most BP levels became normal during the study; much of this effect was due to

TABLE IX Number and Rate (per 1,000 person-years) of Coronary Artery Disease Deaths for Multiple Risk Factor Intervention Trial Participants in the Special-Intervention Group Before April 1, 1980, by Presence of Baseline Electrocardiographic Abnormalities at Rest and by Type and Dose of Diuretic Drug at Last Annual Visit

Drug and Dosage (mg/day)	Baseline Rest ECG Abnormalities: Present			Absent		
	Person-years	Deaths	Rate	Person-years	Deaths	Rate
Chlorthalidone	2,118	7	3.31	4,805	10	2.08
≤50	1,032	5	4.84	2,276	4	1.76
>50	1,086	2	1.84	2,529	6	2.37
Hydrochlorothiazide	2,235	17	7.61	4,969	11	2.21
≤50	1,111	8	7.20	2,644	6	2.27
>50	1,124	9	8.01	2,325	5	2.15
Diuretic other than chlothalidone or hydrochlorothiazide	195	1	5.13	375	0	0.00
No diuretic	4,616	9	1.95	13,061	21	1.61
Total	9,164	34	3.71	23,210	42	1.81

weight reduction or regression toward the mean. A few participants remained hypertensive but refused drug therapy. For the comparison of the relative risk of CAD death (diuretic/no diuretic) among men with ECG abnormalities at rest and men without these abnormalities, this potential bias is minimized, because there is no evidence that compliance or BP lability differs among men with compared to men without ECG abnormalities at rest.

The hypothesis that the relative risk (diuretic/no diuretic) of CAD death differed for SI men with ECG abnormalities compared with SI men without baseline ECG abnormalities at rest was tested using Cox regression models with previously defined covariates (see Design and Methods section). The first model assumed no interaction of diuretic use and baseline ECG abnormalities at rest. The analysis revealed a positive association of each of the entry level risk factors with CAD death, an association of cigarette smoking cessation ($p = 0.01$) and cholesterol reduction ($p = 0.007$) with a decreased CAD mortality, and an association of baseline ECG abnormalities at rest with an increased CAD mortality rate ($p = 0.02$). The association of diuretic use and CAD mortality was positive but not significant ($p = 0.07$). The second model allowed the association of diuretic use with CAD death to vary according to the presence of ECG abnormalities at rest (i.e., an interaction was postulated). Coefficients for the risk factors and their changes were virtually identical to the first model. However, this model indicated that the association of diuretic use with death from CAD depended on the presence of ECG abnormalities at rest ($\chi^2(1) = 8.90$, $p = 0.003$ for interaction). In the presence of ECG abnormalities at rest, the estimated relative risk of CAD for men prescribed a diuretic drug compared with men not prescribed a diuretic drug was 3.34. The corresponding relative risk estimate for men without ECG abnormalities at rest was 0.95. The relative risks estimated from such models separately for men hypertensive and nonhypertensive at baseline were similar. For hypertensive participants the interaction between diuretic use and ECG abnormalities at rest was significant ($p < 0.001$), while for men nonhypertensive at baseline it was not ($p = 0.30$).

In similar models with a term for change in diastolic BP instead of an indicator variable for diuretic, there was a trend in the SI group for BP reduction to be positively associated with an increased CAD mortality rate, but this association is not significant for either ECG subgroup (with abnormalities, $p = 0.15$; without abnormalities, $p = 0.40$).

In the UC group no significant interaction between diuretic treatment and ECG abnormalities at rest was found in men hypertensive at baseline ($p = 0.73$). The estimated relative risk of CAD death (diuretic/no diuretic), adjusted as in the analysis of SI mortality, was 1.25 for men with and 1.09 for men without ECG abnormalities at rest.

As already noted, there were major differences in the use of specific diuretic drugs and their dosage between the SI and UC group. The majority of UC participants receiving antihypertensive drugs were treated with hydrochlorothiazide. Many others were receiving similar thiazide diuretics, and at most annual examinations fewer than 10% were taking chlorthalidone. Most of those receiving hydrochlorothiazide were prescribed doses of 25 to 50 mg/day; for example, at the third annual visit, 34% of those taking hydrochlorothiazide were taking 25 mg and 53% were taking 50 mg.

In the SI group, the protocol permitted use of either hydrochlorothiazide or chlorthalidone, and over the course of the trial MRFIT clinicians used each with about the same frequency. Hydrochlorothiazide was used somewhat more often during the first 5 years, and chlorthalidone much more during the final 2 years as a result of the protocol change previously described. As to dose, SI participants were approximately equally divided between those taking 50 mg and those taking 100 mg of either diuretic through the fifth year.

The results of a person-years analysis relating CAD mortality to specific diuretic and dose levels, and to ECG abnormalities at rest, are shown in Table IX. For this analysis the follow-up period was terminated at March 31, 1980, a point at which approximately half of the conversion to chlorthalidone had occurred for SI participants previously prescribed hydrochlorothiazide. Use of this shortened follow-up period reduces the potential bias in comparing diuretics that could arise if a

TABLE X Mean Serum Potassium Levels and Percent of Participants in Each Group with Potassium Levels of Less Than 3.5 mEq/liter at 48 Months by Type and Dosage of Diuretic Prescribed for Multiple Risk Factor Intervention Trial Participants

	SI			UC		
	No.	Mean (mEq/l)	% <3.5 (mEq/l)	No.	Mean (mEq/l)	% <3.5 (mEq/l)
No antihypertensive drugs	2,487	4.5	0.0	3,351	4.5	0.0
Any treatment	3,256	3.8	21.8	2,306	4.1	10.5
Chlorthalidone						
≤50 mg	506	3.7	31.3	176	3.8	23.5
>50 mg	611	3.6	39.8	68	3.6	45.6
Hydrochlorothiazide						
≤50 mg	935	4.0	10.9	1,214	4.1	5.7
>50 mg	880	3.8	22.4	180	3.7	30.6
Other drugs	324	4.4	3.1	668	4.2	7.0

particular diuretic was associated with an increased risk of CAD and that increased risk was not eliminated when the switch in drugs occurred. For men with ECG abnormalities at rest, the death rate for those taking hydrochlorothiazide at their last visit was 2.30 times higher than for men taking chlorthalidone. After adjustment by Cox regression for age, entry levels of the 3 risk factors, change in serum cholesterol and smoking cessation, the relative risk of hydrochlorothiazide to chlorthalidone was reduced to 1.90 ($p = 0.16$ for difference from 1.0).

For neither diuretic was there a trend toward increasing mortality rate at the higher doses in the presence of ECG abnormalities (Table IX). The Cox-regression-adjusted relative risks (>50 mg/≤50 mg) in the presence of ECG abnormalities were not significantly different from unity (chlorthalidone, 0.73; hydrochlorothiazide, 1.07). Dose was classified at the most recent annual visit; therefore, these relations could have been distorted by reduction of dose between annual visits because of symptoms or biochemical changes.

Several other explanations have been explored as to the apparent interaction between baseline ECG abnormalities and antihypertensive treatment in SI participants. The positive associations by Cox regression analysis between reduction in diastolic BP and CAD mortality in those with and without ECG abnormalities at rest were not significant, and there was no evidence for an interaction with ECG abnormalities. As to the use of other antihypertensive drugs, each of the step II drugs except for methyldopa was used more frequently in SI than UC participants, regardless of the presence of ECG abnormalities at rest (Table I). Moreover, the interaction between diuretic use and ECG abnormalities within the SI group was not affected by whether men were taking diuretics alone or in combination with another drug (largely the antiadrenergic step II drugs).

Possible mechanisms: Among the mechanisms suggested for the apparent adverse effect of diuretics in SI participants with ECG abnormalities at rest, the relation with hypokalemia has been the most extensively examined. Among participants taking antihypertensive drugs, the mean serum potassium level was slightly lower and prevalence of hypokalemia (serum potassium level less than 3.5 mEq/liter) was considerably higher in the SI than in the UC group; prevalence was twice as high at the fourth annual exam (Table X). This greater frequency of hypokalemia is explained by the higher doses of diuretic drugs used by men in the SI compared with the UC group and the greater use of chlorthalidone, more of a potassium-wasting drug than hydrochlorothiazide.

There was no association of hypokalemia (potassium level less than 3.5 mEq/liter) with CAD mortality in the SI group (Table XI), either for all men receiving antihypertensive drug therapy or for those with baseline ECG abnormalities: The prevalence of hypokalemia in all CAD deaths at their last annual visit was 15.7%, in those with ECG abnormalities at rest, 13.2%, and in survivors at 48 months, 23.0%. Previous tables have suggested different degrees of association of hydrochlorothiazide and chlorthalidone with hypokalemia and with CAD mortality; therefore, the data were also stratified by specific diuretic. Among participants taking each drug the numbers of deaths in men with hypokalemia at the last annual visit were few, but there was no indication of a higher prevalence of hypokalemia in men with ECG abnormalities who died than in similarly treated survivors (Table XI).

Because sudden death within 60 minutes accounted for much of the SI-UC difference in CAD mortality, analyses were undertaken of MRFIT data on arrhythmias identified on ECG tracings during annual visits. They have not suggested any association between baseline ECG abnormalities and cumulative incidence of any ventricular premature beats (VPBs) in men hypertensive at entry. Specifically, the incidence of VPBs was no different in hypertensive SI men with ECG abnormalities (10.8%) than in corresponding UC men (10.2%) or in hypertensive SI men who were free of ECG abnormalities (10.4%). The same was true when VPBs constituted at least 10% of recorded beats. However, VPB incidence in the SI hypertensive subgroup as a whole was higher than in UC hypertensive men (relative risk = 1.14); this contrasts with the relative risk (SI/UC) in nonhypertensive men (relative risk = 0.83; $p = 0.008$, for difference in relative risk estimates). Within-group analysis showed a positive association between diuretic use and VPB incidence among SI participants ($p = 0.05$)

TABLE XI Presence of Hypokalemia (Potassium Level Less than 3.5 mEq/liter, Most Recent Annual Visit) for Coronary Artery Disease Decedents and Survivors in the Special-Intervention Group at 48 Months of Follow-Up by the Presence of Baseline Electrocardiographic Abnormalities at Rest

	CAD Deaths						Survivors at 48 Months			
	Rest ECG Abnormalities Absent			Rest ECG Abnormalities Present			Rest ECG Abnormalities Absent		Rest ECG Abnormalities Present	
		K <3.5 mEq/l			K <3.5 mEq/l		K <3.5 mEq/l		K <3.5 mEq/l	
Drug	No. of Deaths	No.	%	No. of Deaths	No.	%	No.	%	No.	%
Any diuretic	32	6	18.8	38	5	13.2	489	23.1	214	22.3
Hydrochlorothiazide	13	1	7.7	21	2	9.5	209	16.9	90	15.6
Chlorthalidone	16	5	31.3	14	2	14.3	278	35.4	123	37.1
Other diuretic, without chlorthalidone or hydrochlorothiazide	3	0	0.0	3	1	33.3	2	2.2	1	1.9

CAD = coronary artery disease.

by Cox regression with adjustment for age, the 3 risk factors at entry, smoking cessation and serum cholesterol change. However, the relative risk of CAD death after VPBs at any previous annual examination was not significantly different from unity for men with (1.24, p = 0.63) or without (1.15, p = 0.79) baseline ECG abnormalities at rest.

Discussion

The purposes of this report were to examine 1 of the 2 major MRFIT subgroup hypotheses, to explore data relevant to an apparent adverse effect related to this hypothesis, and to relate the findings to the overall MRFIT results. Before discussing the results from these perspectives, the strengths and limitations of the data must be considered. The hypothesis regarding the subgroup with a normal ECG at rest, as well as the main data analyses, were determined before the termination of the trial, as were the definitions of abnormal ECG responses at rest and during exercise. However, because subsequent analyses were in part suggested by inspection of the data, there is a greater possibility that the findings represent random variation. Moreover, a number of the critical analyses yielded probabilities that did not achieve nominal levels of significance even without adjustment for multiple subgroup comparisons. Also, although the initial analyses preserved the advantages of randomization, some of the analyses were carried out within the SI or UC groups using postrandomization factors. These are susceptible to bias due to confounding variables, although adjustment for known potential confounders did not weaken the findings.

A further problem with subgroup analyses in MRFIT derives from the fact that the observed numbers of deaths was far lower than expected based on the original study design. Several reasons have been given for this low mortality rate, including the volunteer effect, selection criteria, secular trends, and risk factor changes in both the SI and UC groups.[1] This smaller number of events reduced the statistical power to detect significant associations in subgroups, as it did for the overall trial results. Nevertheless, the findings reported herein suggest important effects of antihypertensive treatment that must be carefully considered.

Baseline-defined subgroups: The test of the hypothesis that in men without ECG abnormalities at rest, CAD mortality would be lower in the SI than UC group yielded suggestive, but not conclusive, results. When examined in the context of findings on the electrocardiogram during exercise, it appears that the very low mortality (compared with overall design expectations) for those with a negative exercise test response is a possible explanation for the failure to identify a substantial SI-UC difference in CAD mortality (Table VII). The mortality rate in the UC group was low among patients without a positive exercise test response, ranging from 8 to 17/1,000 over an average of 7 years among the subgroups, or approximately 1 to 2.5/1,000 per year. It would have required an unusual intervention effect to reduce the CAD mortality rate much below this level; on the same principle, any potential adverse effect may be more readily manifest. A major benefit from intervention was suggested only for men with an abnormal exercise ECG response, a group for which the CAD mortality was much higher than the group with a normal ECG response; details of these results, along with discussion of the pathophysiology of rest vs exercise ECG abnormalities, are the subject of a separate report.[2]

In men without ECG abnormalities during exercise, the SI-UC difference in CAD mortality in hypertensive men with ECG abnormalities at rest was 2.5-fold (row 2, Table VII). Interpretation of these differences involves assessment of the meaning of the unusually low rates in the UC hypertensive subgroup with ECG abnormalities at rest compared with UC men without ECG abnormalities at rest (e.g., 8.2/1,000 and 17.0/1,000 respectively, for those with a normal exercise ECG response). This observation contrasts with previous studies[16] that demonstrated an independent positive relation of similarly defined ECG abnormalities with CAD incidence. These studies have not stratified analyses by hypertensive status, but recently published data from the Chicago Heart Association Detection Project in Industry show a strong prognostic effect of ECG abnormalities on CAD and total mortality in hypertensive men demographically similar to MRFIT participants.[17] These relations clearly need more epi-

demiologic study, but several observations militate against dismissing the MRFIT data on the basis of this inconsistency between findings in the UC group and results of other studies: (1) The more numerous exclusions on the basis of medical history and ECG criteria in MRFIT, compared with observational cohort studies, may alter the distribution and prognostic significance of ECG abnormalities at rest in this selected group of men. (2) More intensive treatment of hypertension than existed in the general community during the 1960s and early 1970s, as occurred in both SI and UC groups, may modify the "natural history" relations. (3) Among SI men, nonhypertensive at entry, ECG abnormalities also exhibited little prognostic significance (Table IV), particularly in the absence of subsequent diuretic therapy—2.0 vs 1.8 CAD deaths per 1,000 person-years (Table VIII). (4) The within-group analyses are strongly suggestive of an unfavorable effect of antihypertensive treatment with diuretics in the SI subgroup with baseline ECG abnormalities at rest.

Antihypertensive drug treatment: There was a significant interaction ($p = 0.003$) between ECG abnormalities at rest and diuretic therapy in the total SI group, an effect that was not evident among UC participants. Results of within-group analyses among SI men using univariate (person-years) and multivariate (Cox regression) methods were consistent. Furthermore, the regression analyses, incorporating terms for the major risk factors at baseline as well as serum cholesterol change and smoking cessation, showed significant associations with CAD risk in expected directions, thereby increasing confidence in the model. In men in the SI group, the association among ECG abnormalities at rest, diuretic treatment and CAD death appeared consistent for both those with baseline hypertension and those with normal BP at entry, a substantial proportion of whom later became eligible for antihypertensive drug treatment. There was a suggestion of a stronger adverse effect of hydrochlorothiazide than chlorthalidone, but the difference did not achieve nominal significance in this analysis.

The evidence regarding the important question of a dose-effect was conflicting, and resolution is difficult, in part because there was considerable shifting of both dose and type of diuretic in SI participants during the trial. Since BP was controlled in the UC group reasonably well, often with a dose of hydrochlorothiazide of less than 50 mg (compared with 50 to 100 mg in the SI group), and no adverse interaction with ECG abnormalities was seen, a reasonable inference may be that the adverse effect in SI men was dose-related. However, there is no indication of dose-relatedness in the SI group from the analyses based on recent visits discussed in this paper, nor from analyses based on dose at a single annual exam early in follow-up (to allow for the possibility of a long latent period). These findings present an unresolved paradox: If not explained by the different dose distributions, why is the interaction of diuretic use and ECG abnormalities at rest not apparent in the UC group? If there is a dose effect, why can it not be detected in the SI group? One possible explanation is that the dose range in the SI group was too limited, since a 25-mg dose was not used. Differential adherence may be another factor; although UC men also reported frequent prescription of a 50-mg dose of hydrochlorothiazide, adherence to the prescribed regimen may have been less than that in the SI group. Finally, since data on UC drug treatment came largely from self-reports, it is probably less reliable than that for the SI group.

If the excess CAD and total mortality in this SI subgroup is real, the mechanism of action is not clear. In other studies, diuretic therapy has been associated with ventricular arrhythmias[18,19] and with sudden death among persons with preexisting heart disease.[20] Whether these relations depend upon hypokalemia is unclear.[19] Hypokalemia was more common in SI than UC participants receiving antihypertensive treatment, but in the analysis using potassium levels at the last annual visit, no relation to CAD mortality was demonstrated. Potassium levels were measured every 4 months and tended to be relatively stable over time. However, transient and unmeasured decreases in serum potassium may have occurred due to unusual environmental stimuli, as has been observed with experimental administration of epinephrine,[21] thus eliciting fatal arrhythmias in susceptible MRFIT men.

The predominance of sudden death within 1 hour as the main category showing an SI-UC difference in cause of death lends some credence to such a mechanism. Another basis for arrhythmic death may be a positive relation between diuretic therapy and blood levels of catecholamines, as reported by other investigators.[22] Although no differences in frequency of VPBs on annual electrocardiograms between SI and UC participants with baseline ECG abnormalities at rest or between SI men with and without abnormalities have been found, there was an apparent excess of VPBs in hypertensive participants in the SI group, and an association with diuretic use. This may have operated upon the background of baseline ECG abnormalities at rest to result in the difference of sudden deaths. The analyses reported do not support this hypothesis, but because ventricular ectopic activity is extremely variable over time[23] and extended ECG monitoring was not performed, the ability to test such a hypothesis is limited.

Various effects of diuretic drugs, as well as of other antihypertensive agents, on blood lipids have been extensively documented, and some of these could theoretically accelerate atherogenesis.[24] Diuretic treatment appeared to affect blood lipids in MRFIT,[25] although mean levels of blood lipids during follow-up were lower in SI than UC participants, except for equal levels of high-density lipoprotein cholesterol.[1] However, SI-UC differences regarding changes in lipid levels did not differ by the presence or absence of ECG abnormalities (Table I); furthermore, in hypertensive men in the SI group, the strength of the association between reduction in the serum cholesterol level and CAD mortality did not differ significantly according to presence or absence of ECG abnormalities.

How do these observations compare with results of other clinical trials? Few data are directly relevant. The efficacy of drug therapy for hypertension has been

documented in several clinical trials.[5,26,27] Much of the reduction in mortality rate has been related to primary hypertensive complications of stroke, congestive heart failure and ruptured aneurysm. There were relatively few deaths from these causes in MRFIT (fewer than 8% of all deaths), probably related to the modest degree of hypertension at baseline, the age group selected, and entry exclusions.[1] The MRFIT results cannot be used as a test of the efficacy of drug therapy in reducing such complications. The results rather relate mainly to the effects of antihypertensive treatment on CAD mortality, an effect in which benefit has not been conclusively shown in the published data from clinical trials.[5,26–29] In this regard, it is relevant that all these trials except for Hypertension Detection and Follow-up Program were low in power to test efficacy of antihypertensive drug treatment in preventing CAD death, and that findings of most, including MRFIT in the subgroup free of ECG abnormalities at rest, showed positive trends. The Hypertension Detection and Follow-up Program has recently reported a significant reduction in indexes of CAD in its stepped-care compared to referred-care group; the data for nonfatal myocardial infarction largely reflect self-reported events.[30]

The MRFIT cohort differed from previous study groups in several respects: The sample was not population-based, as in Hypertension Detection and Follow-up Program; most persons with major end-organ damage were excluded; there were few nonwhite persons and no women. However, the trial may have identified a subgroup of men likely to have a reduced benefit or adverse effect of diuretic therapy. Another controlled trial in a small sample of older men has suggested an adverse effect on CAD mortality of a thiazide diuretic, but this association was not examined with respect to ECG abnormalities or other risk characteristics.[31] Preliminary data from the Hypertension Detection and Follow-up Program have suggested no evidence of harm with respect to all-cause mortality, but an attenuation of benefit from stepped-care in the subgroup with hypertension in the 90 to 104-mm Hg diastolic range, with ECG abnormalities at rest and free of other end-organ damage.[32] The results of the large, placebo-controlled Medical Research Council Trial of Mild Hypertension, in which the active treatment alternatives are thiazide diuretic and a β-adrenergic blocker, may yield data that will further clarify these issues.[33]

Conclusions and Implications

(1) In an analysis based on a prior subgroup hypothesis, a 21% lower CAD mortality rate was found for SI compared to UC participants without baseline ECG abnormalities at rest ($p = 0.12$). The difference in the relative risks (SI/UC) between the subgroups with and without ECG abnormalities at rest suggested that risk factor intervention was more effective for men without than with abnormalities ($p = 0.08$ for difference in relative risk estimates).

(2) This finding was not a result of confounding by differential risk factor intervention (SI vs UC) according to the presence or absence of ECG abnormalities (Table I).

(3) The increased risk of CAD death (SI vs UC) among men with ECG abnormalities at rest was concentrated in participants who were hypertensive at baseline. The estimated adjusted relative risk of CAD death (SI/UC) was 1.67 for hypertensive men with ECG abnormalities at rest (Table II).

(4) High R waves were the most common ECG abnormalities, but these and other BP-associated codes were not differentially associated with higher CAD mortality rate in the SI group when compared with all other ECG abnormalities (Tables III, IV).

(5) The higher relative risk (SI/UC) of CAD mortality for men with ECG abnormalities at rest was not confined to a particular level of entry BP (Table V).

(6) The association of ECG abnormalities at rest and CAD mortality was manifested chiefly as sudden deaths within 60 minutes of being seen alive and apparently well (Table VI).

(7) The CAD mortality rate was lower in the SI than in the UC subgroup with both abnormal rest and exercise ECG responses (Table VII). However, the relation of CAD mortality with ECG abnormalities at rest appeared to be independent of the presence or absence of an abnormal exercise ECG, i.e., the relative effect on the risk ratio (SI/UC) was approximately the same among men with as in those without exercise ECG abnormalities, in that ECG abnormalities at rest were associated with some attenuation of the apparent SI benefit (compared with UC) in the presence of exercise-associated ECG abnormalities.

(8) A significant positive association of CAD mortality with the joint presence of ECG abnormalities at rest and diuretic treatment was found in the SI (Table VIII) but not the UC group. This interaction could not be explained by the amount of BP reduction or the use of other antihypertensive agents. There was a nonsignificant trend ($p = 0.16$) toward a greater association of increased CAD mortality with the use of hydrochlorothiazide than of chlorthalidone among men with ECG abnormalities at rest (Table IX).

(9) Based on several definitions of exposure, no association of CAD mortality in the SI group with dose of either diuretic could be found (Table IX).

(10) Hypokalemia was more frequent among men in the SI than in the UC group receiving diuretic treatment, but no more frequent at their last annual visit in SI men who died of CAD while on drug treatment than in survivors, irrespective of ECG abnormalities at rest (Tables X and XI). Hypertensive participants also had an increased relative risk (SI/UC) of VPBs compared with nonhypertensive men, but there was no difference based on ECG abnormalities at rest. Finally, there was no significant association between VPBs and CAD mortality.

The MRFIT findings relative to ECG abnormalities at rest emerged from further pursuing the results of analyses planned before the data were examined, and are thus not conclusive. However, they should be regarded as indicating a need for review and reassessment of therapeutic approaches for a subgroup of patients with less severe hypertension and ECG abnormalities at rest. Such reassessment should consider choices of

drugs and dosage, drug combinations, and the appropriate role of nonpharmacologic management as sole and as adjunctive therapy.

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Appendix

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The principal investigators and senior staff of the clinical, coordinating, and support centers, the National Heart, Lung, and Blood Institute, and members of the MRFIT Policy Advisory Board and Mortality Review Committee are:

American Health Foundation, New York: Charles Arnold, MD, MPH (principal investigator), Rebecca Mandriota, MS, MEd, Richard Ames, MD, Joan Ruff Eisenbach, RN.

Boston University, Boston: H. Emerson Thomas, Jr, MD (principal investigator), William Kannel, MD (co-principal investigator), L. Kent Smith, MD, Charles Deckman.

Cox Heart Institute, Kettering, Ohio: Paul Kezdi, MD (principal investigator), Edwin Stanley, MD (co-principal investigator), Frederick Ernst, PhD, E. Jean Case, RN, MS.

Dade County Department of Public Health, Miami: George Christakis, MD, MPH (principal investigator), Janice Burr, MD (co-principal investigator), Terence Gerace, PhD (co-principal investigator), Mary Ellen Wilcox, RD, MEd.

Dalhousie University Halifax, Nova Scotia (MRFIT ECG Center): Pentti Rautaharju, MD, PhD (principal investigator), Hermann Wolf, PhD.

Harvard University, Boston: Robert Benfari, PhD (principal investigator), Kevin McIntyre, MD, JD (co-principal investigator), Oglesby Paul, MD (co-principal investigator; former chairperson, Steering Committee), Elinor Danielson, MA, Judith Ockene, PhD.

Kaiser Foundation Research Institute, Portland, Oregon: John Wild, MD (principal investigator), M. R. Greenlick, PhD (co-principal investigator), John Grover, MD (co-principal investigator), Sara Lamb, Jeffry Bailey, Judith Dyer, MSHyg, RD, Barbara Brokop, RN, Victor Stevens, PhD, Geraldine Bailey, RN.

Lankenau Hospital, Philadelphia: William Holmes, PhD (principal investigator), J. Edward Pickering, MD (co-principal investigator), James Allaire, MEd, Diane Fellon, RN, Barbara Feinstein, MSA, Diana Hutchins, MD.

National Center for Disease Control, Atlanta: Gerald Cooper, PhD, MD (principal investigator).

New Jersey Medical School, Newark: Norman Lasser, MD, PhD (principal investigator), Norman Hymowitz, PhD (co-principal investigator).

Northwestern University, Chicago: Jeremiah Stamler, MD (principal investigator), Dorothy Moss, MS, RD, Victoria Persky, MD, Linda Van Horn, PhD, RD, Kay Shannon, MA, David Meyers, MD.

University of Chicago, Chicago: Louis Cohen, MD (principal investigator), Juliet Morgan, PhD (co-principal investigator), Gayle Grundmann, MS, RD, Thomas Vestal, PA, Ben Huang.

St. Joseph's Hospital, Chicago: David Berkson, MD (principal investigator), Gary Lauger, MS, Stevan Grujic, MD, David Obradovic, MD.

Institutes of Medical Sciences–University of California, San Francisco and Berkeley: James Billings, PhD, MPH

(principal investigator), Stephen Hulley, MD, MPH (co-principal investigator), W. McFate Smith, MD, MPH (co-principal investigator), S. Leonard Syme, PhD (co-principal investigator), Richard Cohen, MS, Lisa Dzvonik, MA, RD, Leslie Roos, Mary Kahn, RN.

Institutes of Medical Sciences, San Francisco Central Laboratory: Graham Widdowson, PhD (co-principal investigator), George Williams, MD (co-principal investigator), Stephen Hulley, MD, MPH (co-principal investigator).

Rush-Presbyterian-St. Luke's Medical Center, Chicago: James Schoenberger, MD (principal investigator), Joseph Schoenenberg, PhD, Richard Shekelle, PhD, Gilberto Neri, MD, Therese Dolecek, PhD, RD.

Rutgers Medical School, Piscataway, New Jersey: Nicholas Wright, MD, MPH (principal investigator), Steven Kopel, PhD (co-principal investigator), Kenneth Suckerman, PhD, Marilyn Schorin, MPH, RD.

St. Louis Heart Association, St. Louis: Nathan Simon, MD (principal investigator), Jerome Cohen, MD (co-principal investigator), Elizabeth Bunkers, RD.

University of Alabama in Birmingham: Harold Schnaper, MD (principal investigator), Glenn Hughes, PhD (co-principal investigator), Ralph Allen, PA, Phillip Johnson.

University of California, Davis: Nemat Borhani, MD (principal investigator), Carolyn Sugars, RD, Karen Kirkpatrick, Marshall Lee, MD, Frances LaBaw, RN.

University of Maryland, Baltimore: Roger Sherwin, MB, BChir (principal investigator), Mary McDill Sexton, PhD, MPH (co-principal investigator), Quely de Barros, MS, Patricia Dischinger, PhD, Jutta Heiner, MD, Mary Pilkington, RN, MSN, Barbara Scanlon, MA.

University of Minnesota, Minneapolis: Richard Grimm, Jr, MD, MPH (principal investigator), Henry Blackburn, MD (co-principal investigator), Richard Crow, MD (co-principal investigator), Maurice Mittelmark, PhD (co-principal investigator), Mary McDonald, RN, MS.

University of Minnesota ECG Coding Center, Minneapolis: Ronald Prineas, MB, PhD (director), Richard Crow, MD (associate director).

University of Minnesota Nutrition Coding Center, Minneapolis: Ida Buzzard, PhD (director), Joyce Wenz, MS, RD (associate director).

University of Minnesota Coordinating Center, Minneapolis: Marcus Kjelsberg, PhD (principal investigator), Glenn Bartsch, ScD (co-principal investigator), James Neaton, PhD (co-principal investigator), Steven Broste, MS, John Connett, PhD, Alain DuChene, Diane Gorder, MS, Gregory Grandits, MS, Kenneth Svendsen, MS.

University of Pittsburgh, Pittsburgh: Lewis Kuller, MD, DPH (principal investigator), Robert McDonald, MD (co-principal investigator), Lorita Falvo-Gerard, MN, MPH (co-principal investigator), Arlene Caggiula, PhD, RD (co-principal investigator), Elizabeth Gahagan, RN, Roberta Moyer, RN, Mary Alman, RN, Karen Southwick, ASCP.

University of South Carolina, Columbia: Warren Giese, PhD (principal investigator), J. Frank Martin, MD (co-principal investigator), James Keith, PhD (co-principal investigator), Harriet Harrison, RN.

University of Southern California, Los Angeles: Eugene Fishman, MD (principal investigator), Laurence Wampler, PhD, Gretchen Newmark, MA, RD, Shahida Siddiqui, MD, Lauren Paquet, RN.

Policy Advisory Board: William Insull, Jr, MD (chairperson), John Farquhar, MD, C. David Jenkins, PhD, Elliot Rapaport, MD, Donovan Thompson, PhD, Herman Tyroler, MD, Park Willis III, MD, William Friedewald, MD (ex officio), William Zukel, MD (ex officio).

Mortality Review Committee: Joseph Doyle, MD (chairman), Howard Burchell, MD, Paul Yu, MD, Park Willis III, MD (former member).

National Heart, Lung, and Blood Institute Staff, Bethesda, Maryland: William Friedewald, MD (program director), Curt Furberg, MD (project office director), Jeffrey Cutler, MD (scientific project officer), William Zukel, MD (former program director), Eugene Passamani, MD (former scientific project officer), Charles Kaelber, MD (former scientific project officer), Joel Verter, PhD, Margaret Wu, PhD.

Exercise Electrocardiogram and Coronary Heart Disease Mortality in the Multiple Risk Factor Intervention Trial

MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP

The Multiple Risk Factor Intervention Trial (MRFIT), a coronary heart disease (CAD) primary prevention trial, examined the effect on the CAD mortality rate of a special intervention (SI) program to reduce blood cholesterol level, diastolic blood pressure and cigarette smoking in 35- to 57-year-old men. Half of the 12,866 participants were randomly assigned to usual care (UC) in the community. During 6 to 8 years of follow-up, the CAD mortality rate was 7% lower in the SI than in the UC group, a nonsignificant difference. An a priori subgroup hypothesis proposed that men with a normal electrocardiographic response to a heart-rate-limited exercise test would experience particular benefit from intervention. An abnormal response, defined as an ST-depression integral measured by computer greater than a predetermined voltage-time cutpoint, was observed in 12.5% of the men at baseline, and was associated with a 3-fold elevation in risk of CAD death within the UC group. In the subgroup with a normal exercise electrocardiographic response, there was no significant SI-UC difference in the CAD mortality rate (16.0 and 13.8 per 1,000, respectively, for SI and UC men). In contrast, there was a 57% lower rate among men in the SI group with an abnormal test result compared with men in the UC group (22.2 vs 51.8 per 1,000). The relative risks (SI/UC) in these 2 strata were significantly different ($p = 0.002$). These findings suggest that men with elevated risk factors who have an abnormal exercise test response may benefit substantially from risk factor reduction. (Am J Cardiol 1985;55:16–24)

The Multiple Risk Factor Intervention Trial (MRFIT) was a randomized primary prevention trial designed to test the effect of a multifactorial intervention program on the mortality rate from coronary heart disease (CAD) in 12,866 men aged 35 to 57 years. The previously reported mortality results of the MRFIT showed a nonsignificant 7% lower CAD mortality rate in the special-intervention (SI) compared with the usual-care (UC) group.[1]

Two major subgroup hypotheses related to the baseline electrocardiograms (ECGs) were formulated in the early stages of the trial. These were set out to test whether favorable SI-UC differences in CAD mortality and morbidity could be demonstrated in men who at entry into the trial had a normal ECG response at rest or a normal ECG response to exercise, respectively. These 2 subgroup hypotheses were based on the idea that in a primary prevention trial in men at high risk free of clinical CAD, intervention at an earlier phase of the evolution of CAD would be more effective than at a later (even though preclinical) phase of the disease. The subgroup analyses related to the ECG at rest are presented in a separate report.[2]

The objective of this report is to address the other subgroup hypothesis: Among men with a normal electrocardiographic response to exercise, the incidence of CAD death is significantly lower in the SI compared with the UC group. The analyses are based on computer-read exercise ECGs. Since their clinical value is not well established, the prognostic significance of a positive exercise response in the UC group is also presented. Because the main MRFIT findings regarding morbid CAD events have not yet been reported, analyses in this paper are confined to fatal CAD.

Methods

Study population: MRFIT was a randomized clinical trial that involved screening during 1973 to 1976 of 361,662 men, aged 35 to 57 years, at 22 participating clinical centers in the U.S. A total of 12,866 men without evidence of definite CAD by history, physical examination or ECG at rest were enrolled in the trial. The eligibility criteria, statistical design consid-

The Participating investigators and their institutional affiliations are listed in the Appendix. Manuscript received July 23, 1984; revised manuscript received September 10, 1984, accepted September 11, 1984.

Address for reprints: Marcus O. Kjelsberg, PhD, MRFIT Coordinating Center, Biometry Division, University of Minnesota School of Public Health, Room 508, 2829 University Avenue Southeast, Minneapolis, Minnesota 55414.

erations, and methods have been described.[1,3] The selection criteria included the use of a multiple logistic risk function, derived from Framingham data, to estimate each prospective participant's risk of future CAD on the basis of serum cholesterol concentration, diastolic blood pressure and cigarette smoking. Men were screened to select those in the upper 15% (later 10%) of a risk score distribution based on Framingham data. During screening, men with evidence of CAD, serious life-limiting conditions, markedly elevated diastolic blood pressure (≥115 mm Hg), or very high serum cholesterol levels (≥350 mg/dl) were excluded from the trial. Certain electrocardiographic abnormalities at rest including major Q waves and complete bundle branch block, as well as the use of digitalis drugs, were additional reasons for exclusion.

MRFIT participants were randomly assigned to either of 2 groups: a special-intervention program (the SI group) consisting of counseling for cessation of cigarette smoking, advice on dietary practices to lower blood cholesterol level, and stepped-care drug treatment for hypertension; or a group referred to their customary sources of health care in the community (the UC group).

Electrocardiographic recording and analysis methods: ECGs were recorded at rest and during exercise directly on FM cassettes using Marquette 3500 recorders. The ECG at rest obtained at baseline and annually included 15 electrocardiographic leads: 12 conventional leads and the orthogonal XYZ Frank leads. Because of the requirement to record ECGs both at rest and during exercise in the same session, the commonly used modified limb electrode positions were used to record the 12-lead ECGs.[4] The modification involved location of the left and right arm electrodes in the infraclavicular fossae 2 cm below the lower border of the clavicle and medial to the border of the deltoid muscle. The left leg electrode was placed at the horizontal level of the iliac spine in the midclavicular line (below electrode V_4). This modification induced significant changes in the frontal plane QRS axis and limb lead ECG waveforms.[4] However, it was adopted to obtain a higher quality ECG during exercise.

The 9 leads chosen for exercise stress testing were CS_5, aVL, aVF, V_4, V_5, V_6, X, Y and Z. Recordings were obtained immediately preceding the exercise test, during the peak exercise state, during the immediate recovery state, and 3 minutes after termination of exercise. All nonexercise tracings were recorded with the participant in a sitting position. Each sequence of exercise leads was recorded for 10 seconds, 3 leads at a time.

A graded treadmill exercise test was performed with stepwise increase of the slope and speed until a target heart rate predetermined for each man was reached or until the test was terminated prematurely because of symptoms. Target heart rates were 160, 157, 155, 153 and 151 beats/min for the age groups 35 to 39, 40 to 44, 45 to 49, 50 to 54 and 55 to 57 years, respectively. These rates were based on the predicted 84% of maximal heart rate for men of this age.[5] The only reason for deviation from the exercise protocol was for early termination of the test. Reasons for early termination, if this occurred, were recorded as follows: inability to continue; observed ST-segment depression reaching 0.1 mV at 80 ms past the J point; certain arrhythmias; systolic blood pressure exceeding 250 mm Hg; decrease in systolic pressure with increasing level of exercise; and technical problems. The men were instructed to refrain from smoking for at least 1 hour and to fast for at least 2 hours before the test. The average fasting time was approximately 6 hours.

The FM cassettes recorded at the clinical centers were sent to the ECG center in Halifax, where the ECGs were analyzed by a computer program. Prefiltering was used with upper corner frequency of 125 Hz and a sampling rate of 500 samples/s per channel. Computer analysis was done with an electrocardiographic program that used selective averaging of complexes for noise reduction.[6] An interactive computer-graphics terminal was used to verify the quality of all exercise electrocardiographic data, whereby the operator could easily check computer measurements and reject leads with excessive residual noise.

The computer program analyzed records obtained during the preexercise period, during the last 30 seconds of the peak exercise state, and during both points in the recovery period (immediately and at 3 minutes afterwards).

The criteria for an abnormal (ischemic) electrocardiographic response to exercise, established before any of the present analyses were performed, were as follows: ST-segment depression 16 μV-s or more in peak exercise or immediate recovery records in any of the leads CS_5, aVL, aVF, or V_5, with ST-segment depression less than 6 μV-s in the above leads in the preexercise sitting record.

The ST-segment depression was measured as the voltage-time integral over the negative portion of the ST segment within the initial seven-sixteenths of the ST-T interval (Fig. 1). The voltage-time integral units (microvolt-seconds) can be easily related to conventional visual measurements by estimating the area of ST depression under the PR baseline. For instance, an average ST depression of 0.1 mV (or 100 μV) over a period of 0.10 second is equal to an ST depression integral of 10 μV-s (irrespective of the slope of the ST segment). The choice of seven-sixteenths of the ST-T segment for the upper time limit of this integral was made on an empirical basis: This time point corresponds to the best visual estimate of the de-

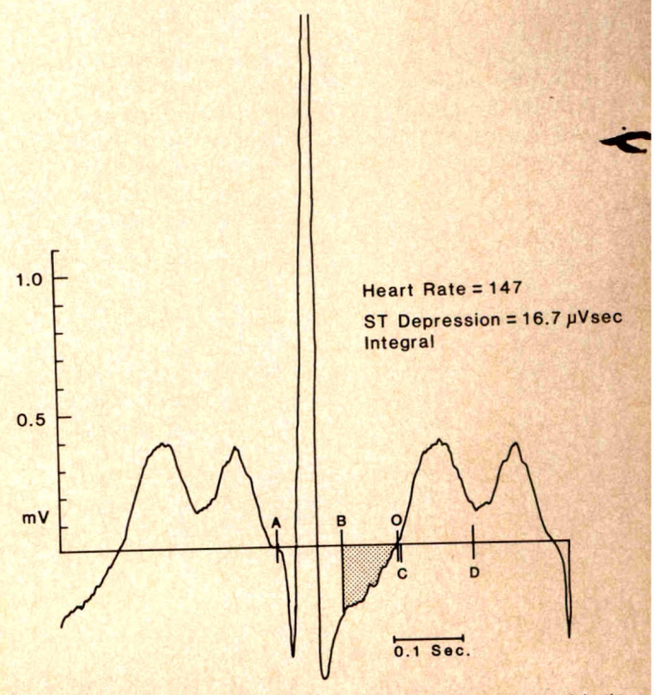

FIGURE 1. Definition of ST-depression integral (**shaded area**) is the time integral (in microvolt-seconds) of the electrocardiographic voltage from the end of QRS (**B**) to the zero crossing (0). If the ST segment is very slowly ascending or has a horizontal or downsloping course, the ST-segment area integration is terminated at the time point corresponding to seven-sixteenths of the total ST-T interval (i.e., BC = 7/16BD). The PR segment (**A**) immediately preceding QRS onset is taken as the baseline reference level for the integration. Measurements are made after clustering of all complexes, filtering and selective averaging.

TABLE I Number and Percent of Participants in the Multiple Risk Factor Intervention Trial Who Performed the Exercise Test and Reached Target Heart Rate and Reasons for Stopping Early

	SI		UC	
	n	%	n	%
No. randomized	6,428	100.0	6,438	100.0
Participated in exercise test	6,217	96.7*	6,205	96.4*
Reached target heart rate	5,176	83.3†	5,149	83.0†
Did not reach target heart rate, stopped early	1,041	16.7†	1,056	17.0†
Reasons for stopping early‡				
Leg discomfort, dyspnea, chest pain, fatigue, gait or speech disturbance	578	55.5	575	54.5
SBP ≥250 mm Hg	85	8.2	115	10.9
SBP decrease with exercise	14	1.3	7	0.7
ST abnormality (as judged by the attending physician)	200	19.2	185	17.5
Other ECG abnormalities (arrhythmias, etc.)	110	10.6	119	11.3
Technical and other problems	74	7.1	63	6.0

* Percent of those randomized.
† Percent of those who had an exercise test. All other percentages are of those who did not reach target heart rate.
‡ More than 1 reason could have been indicated.
ECG = electrocardiographic; SI = special intervention; SBP = systolic blood pressure; UC = usual care.

marcation point between the ST segment and the T wave, whenever it can be distinguished with reasonable repeatability. The 16-μV-s threshold for an abnormal electrocardiographic response to exercise was chosen before any analysis and represents a value 2 standard deviations above the mean for commonly used exercise leads,[6] with an upwards adjustment to account for the higher sensitivity (lead strength) of lead CS_5 used in MRFIT. The requirement that the preexercise ST depression must be less than 6 μV-s implies that the ST segment must increase at least 10 μV-s before it is called abnormal.

The computer ECG center in Halifax also reproduced paper tracings for visual coding. Because of anticipated problems of excessive noise, the visual analysis did not include a standardized reading of the peak exercise records, the customary point for clinical interpretation. Visual readings revealed a very low prevalence (<1%) of abnormalities (Minnesota code 4.1) during the period of recovery after exercise, as anticipated. Therefore, the subgroup findings in this report are restricted to analyses of the more prevalent abnormal test results from computer readings.

Statistical methods: The Kaplan-Meier product limit method[7] was used to compute the cumulative event rates for CAD death. Comparisons of survival (SI vs UC) for the subgroups defined by the presence or absence of abnormal electrocardiographic responses are summarized using the log-rank test.[8]

The Cox proportional hazards model[9] was used to assess the prognostic importance of exercise electrocardiographic abnormalities in the UC group after adjustment for other baseline risk variables. The Cox model was also used to assess the heterogeneity of the relative risk estimates (SI/UC) for men with and men without exercise electrocardiographic abnormalities and by risk factor level at entry.

The difference in risk factor levels and the use of antihypertensive treatment at 48 months between the SI and UC groups with and without abnormal exercise electrocardiographic response are summarized using Student t test for 2 independent samples and the normal approximation to the binomial distribution. Significance probabilities (p values) are unadjusted for multiple comparisons. Two-sided p values <0.05 are termed nominally significant.

Results of subgroup analyses in MRFIT should be viewed with caution, because the number of deaths observed overall was far smaller than expected based on the original study design. This smaller number of events reduces the statistical power to detect significant associations in subgroups.

TABLE II Crude and Adjusted Relative Risk Estimates for Participants in the Usual-Care Group with Exercise Electrocardiographic Abnormalities Compared to Men Without Electrocardiographic Abnormalities

	Crude RR	Adjusted* RR	p Value for Adj. RR	95% CI for Adj. RR
CAD death	3.75	3.44	<.0001	(2.31, 5.12)
All deaths	1.69	1.60	0.005	(1.15, 2.22)

* Using Cox regression for age, diastolic blood pressure, serum cholesterol concentration and number of cigarettes smoked per day.
CAD = coronary heart disease; CI = confidence interval; RR = relative risk.

Results

Of the 12,866 men enrolled, 12,422 (96.6%) participated in the baseline exercise ECG test (Table I). Men were excluded from the test if they had locomotor problems or ST-T changes on their ECG at rest as judged by the attending physician. (Participants with the voltage changes of left ventricular hypertrophy only were not excluded.) For men who had an exercise test, an equally high proportion (83%) in the SI and UC groups reached target heart rate (Table I). Reasons for terminating the test were similar in the 2 groups.

Prevalence of ischemic ST-segment response to exercise: In the group of 12,422 men who participated in the exercise test, the quality of the record was considered adequate for computer analysis in 12,294 participants (99.0%), and their tracings were analyzed. Of these, 276 men had a seven-sixteenths ST depression integral ≥6 μV-s in the preexercise sitting record and, therefore, did not meet the criterion for an abnormal electrocardiographic response to exercise. The overall prevalence of an abnormal ST-segment response to exercise, as a percent of those with available exercise data and a normal ST-segment response at rest, was 12.7% in the SI group and 12.2% in the UC group. This difference in prevalence was not significant. The contribution of various leads to overall prevalence will be addressed by a report in preparation.

TABLE III Number of Coronary Artery Disease Deaths and Cumulative Coronary Artery Disease Mortality Rate per 1,000 by Year of Follow-Up and the Presence or Absence of an Abnormal Exercise Electrocardiographic Response for Participants in the Multiple Risk Factor Intervention Trial*

	Exercise ECG Normal				Exercise ECG Abnormal			
	No. CAD Deaths		Cumulative Mortality per 1,000 Men		No. CAD Deaths		Cumulative Mortality per 1,000 Men	
Year	SI	UC	SI	UC	SI	UC	SI	UC
1	7	6	1.3	1.1	4	2	5.2	2.7
2	6	12	2.5	3.4	3	7	9.2	12.3
3	9	9	4.2	5.1	2	7	11.8	21.8
4	11	10	6.3	7.0	3	5	15.7	28.7
5	16	5	9.4	8.0	2	10	18.4	42.4
6	15	17	12.3	11.3	1	3	19.7	46.5
6-year total	64	59	—	—	15	34	—	—
As of 2/28/82†	84	73	16.0	13.8	17	38	22.2	51.8
Log rank Z statistic			0.9				−2.8	

* Two hundred eighty-three men in the SI group (9 CAD deaths) and 288 in the UC group (11 CAD deaths) who did not participate in the exercise test and 135 men in the SI group (5 CAD deaths) and 142 in the UC group (2 CAD deaths) with ST depression integral abnormal (≥6 μV-s) in preexercise rest sitting ECG are excluded from this mortality comparison.

† Average follow-up of 7 years.

CAD = coronary heart disease; ECG = electrocardiogram; SI = special intervention; UC = usual care.

Prognostic significance of computer-read exercise electrocardiograms: Men in the UC group with an abnormal ST-segment response to exercise had significantly higher death rates from CAD (51.8 vs 13.8 per 1,000) and from all causes (61.3 vs 36.2 per 1,000) than UC men without such a response. The CAD mortality rate was 3.4 times higher in men in the UC group with an ischemic exercise electrocardiographic response compared with men in the UC group without an ischemic exercise electrocardiographic response, after adjustment for age and baseline risk factors (Table II). The adjusted relative risk for all-cause mortality was 1.6.

Coronary artery disease mortality in SI and UC subgroups with normal electrocardiographic response to exercise: The left side of Table III shows the cumulative CAD mortality rate by year of follow-up among men in the SI and UC groups with a normal electrocardiographic response to exercise according to the computer criteria. At the end of the trial, with an average follow-up of 7 years, the cumulative CAD mortality rate was 13.8/1,000 in the UC group, compared to 16.0/1,000 in the SI group, a difference of +2.2/1,000. This relative SI-UC difference of 15.9% (95% confidence interval of +59.4% to −15.4%) is in a direction opposite to that hypothesized and is not statistically significant.

Coronary artery disease mortality in SI and UC subgroups with ischemic electrocardiographic response to exercise: The right side of Table III shows the cumulative CAD mortality rate by year of follow-up among men in the SI and UC groups with abnormal ECG response to exercise. The mortality rate was 51.8/1,000 among UC men, and 22.2/1,000 in the SI men, a difference of 57% (p = 0.007). The difference in the relative risk estimates (SI/UC) for CAD death for men with a normal exercise electrocardiographic response (1.16) compared with that for men with an abnormal exercise electrocardiographic response (0.43) is statistically significant (p = 0.002).

The cumulative CAD mortality curves are shown in Figure 2 for SI and UC subgroups with and without ischemia on the exercise ECG. After 2 years of intervention there was a sharp divergence in the mortality curves between UC and SI men with an abnormal exercise response.

Detailed causes of death by presence and absence of an abnormal exercise ECG response are given in Table

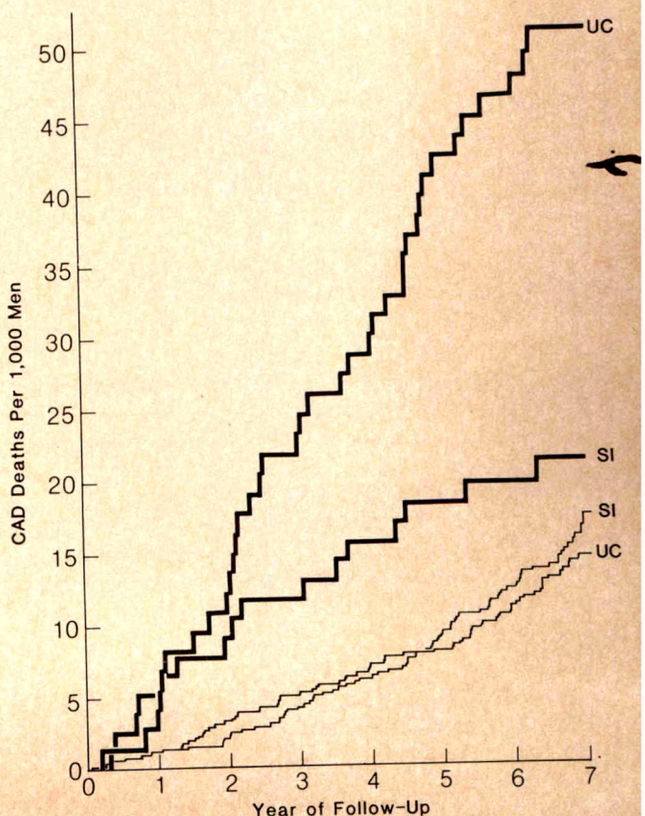

FIGURE 2. Cumulative coronary heart disease (CAD) mortality rates for participants in the Multiple Risk Factor Intervention Trial according to the presence or absence of an abnormal exercise electrocardiographic response. The **heavy line** indicates men with an abnormal baseline exercise electrocardiographic response and the **thin line,** men with normal exercise electrocardiographic response. SI = Special-intervention group; UC = usual-care group.

TABLE IV Number of Deaths by Cause (per 1,000) for Participants in the Multiple Risk Factor Intervention Trial by the Presence of Exercise Electrocardiographic Abnormalities at Baseline

	Exercise ECG Normal				Exercise ECG Abnormal			
	SI		UC		SI		UC	
Cause of Death	n	Rate	n	Rate	n	Rate	n	Rate
CAD	84	16.0	73	13.8	17	22.2	38	51.8
Myocardial Infarction	24	4.6	20	3.8	8	10.5	12	16.4
Sudden death <60 minutes	44	8.4	30	5.7	5	6.5	19	25.9
Sudden death <24 hours but ≥60 minutes	14	2.7	16	3.0	1	1.3	7	9.5
Other CAD	2	0.4	7	1.3	3	3.9	0	0.0
Other cardiovascular disease	19	9.1	17	8.9	3	9.4	2	4.4
Noncardiovascular disease	97	18.5	96	18.2	10	13.1	4	5.5
Unknown	8	1.5	5	1.0	2	2.6	1	1.4
Total	208	39.7	191	36.2	32	41.8	45	61.3

CAD = coronary heart disease; ECG = electrocardiogram; SI = special intervention; UC = usual care.

TABLE V Number of Coronary Artery Disease Deaths and Relative Risk Estimates (Special Intervention/Usual Care) According to the Maximum Level of ST Depression Integral for Participants in the Multiple Risk Factor Intervention Trial*

7/16 ST Depression Integral† (μV-s)	No. Participants		No. CAD Deaths (per 1,000)		Relative Risk (SI/UC)‡
	SI	UC	SI	UC	
<84	1,387	1,425	20 (14.4)	13 (9.1)	1.58
4–7.99	1,830	1,801	23 (12.6)	21 (11.7)	1.08
8–11.99	1,231	1,294	22 (17.9)	22 (17.0)	1.05
12–15.99	796	754	19 (23.9)	17 (22.5)	1.06
≥16	765	734	17 (22.2)	38 (51.8)	0.43
Total	6,010	6,008	101 (16.8)	111 (18.5)	0.91

* Restricted to participants with measurements during at least one stage of exercise.
† See text and Figure I for definition.
‡ p = 0.003 for significant trend in relative risk estimates.
CAD = coronary heart disease; SI = special intervention; UC = usual care.

IV. In the subgroup with abnormal response, the 57% SI-UC difference in CAD mortality is seen to reflect mainly lower SI rates of sudden death. Rates of non-CAD causes of death were somewhat higher in the SI than UC subgroup. However, the total mortality rate was approximately 50% higher in the UC ($p < 0.01$). In the subgroup with normal exercise electrocardiographic response, rates for various causes of death were similar for SI and UC groups.

Table V shows CAD death rates and relative risks (SI/UC) for 5 levels of ischemic ST-segment depression. The CAD death rates tended to increase with increasing levels of ST-depression integral for men in both groups, but more so for men in the UC group. A significant linear trend in the relative risk (SI/UC) estimates was noted ($p = 0.003$). The CAD mortality benefit in the SI relative to the UC group was only seen for maximal (≥16 μV-s) levels of ST-depression integral (relative risk of 0.43).

Relation of rest and exercise electrocardiogram to coronary artery disease and all-cause mortality: CAD and total mortality rates for men in the SI and UC groups with and without resting and exercise electrocardiographic abnormalities are given in Table VI. For men in both groups with normal electrocardiographic responses at rest and during exercise (the largest subgroup) CAD and total mortality rates were remarkably similar. The CAD death rate among UC men with an abnormal exercise electrocardiographic response but a normal electrocardiographic response at rest was 44.4 per 1,000, or about 3 times higher than the rate in the corresponding group of SI men (14.1 per 1,000). The SI rate is similar to that for SI and UC men with normal electrocardiographic responses at rest and during exercise. For men with abnormal exercise and rest electrocardiographic responses, the highest death rates were seen. A 43% lower CAD rate in the SI compared with UC group was not reflected in the total mortality rate. The direction of the SI-UC difference in the subgroup of men with a normal exercise and an abnormal rest electrocardiographic response was unfavorable to the SI group, i.e., the CAD death rates were 20.0 per 1,000 for SI men and 10.6 per 1,000 for UC men ($p = 0.048$).

The data in Figure 2 and Table IV, which document heterogeneity of relative risk (SI/UC) of CAD death according to the presence or absence of exercise electrocardiographic abnormalities, pose a question: Did men in the SI group with abnormal exercise electrocardiographic responses receive different intervention

TABLE VI Number (per 1,000 Randomized Participants) of Coronary Artery Disease Deaths and Deaths from Any Cause by Presence of Rest and Exercise Electrocardiographic Abnormalities for Participants in the Multiple Risk Factor Intervention Trial

Rest ECG	Exercise ECG	No. Participants		CAD Deaths		All Deaths	
		SI	UC	SI	UC	SI	UC
Normal	Normal	3,891	3,950	57 (14.6)	59 (14.9)	152 (39.1)	145 (36.7)
Abnormal	Normal	1,353	1,324	27 (20.0)	14 (10.6)	56 (41.4)	46 (34.7)
Normal	Abnormal	497	473	7 (14.1)	21 (44.4)	12 (24.2)	26 (55.0)
Abnormal	Abnormal	268	261	10 (37.3)	17 (65.1)	20 (74.6)	19 (72.8)
Normal	*	47	57	1 (21.3)	1 (17.5)	1 (21.3)	4 (70.2)
Abnormal	*	88	85	4 (45.5)	1 (11.8)	8 (90.9)	4 (47.1)
Normal	No exercise ECG	167	190	3 (18.0)	7 (36.8)	6 (35.9)	10 (52.6)
Abnormal	No exercise ECG	116	98	6 (51.7)	4 (40.8)	10 (86.2)	6 (61.2)
Total		6,427†	6,438	115 (17.9)	124 (19.3)	265 (41.2)	260 (40.4)

* ST depression integral abnormal (≥6 μV-s) in pre-exercise rest sitting ECG.
† Excludes 1 participant with missing baseline resting ECG.
CAD = coronary heart disease; ECG = electrocardiogram; SI = special intervention, UC = usual care.

TABLE VII Risk Factor Change and Antihypertensive Drug Use at 48 Months for Multiple Risk Factor Intervention Trial Participants According to the Presence of Exercise Electrocardiographic Abnormalities

	Exercise ECG Normal			Exercise ECG Abnormal			Differences in SI-UC Differences (Normal-Abnormal)*
	SI	UC	SI-UC	SI	UC	SI-UC	
Serum cholesterol change (mg/dl)	−18.4	−10.3	−8.1	−19.6	−8.9	−10.7	2.6
LDL change (mg/dl)	−11.6	−6.2	−5.4	−11.0	−5.9	−5.1	−0.3
HDL change (mg/dl)	0.8	1.0	−0.2	0.2	0.2	0.0	−0.2
Triglycerides change (mg/dl)	−6.9	0.7	−7.6	−5.4	6.8	−12.2	4.6
Weight change (lbs)	−4.2	−3.7	−0.5	−4.3	−3.7	−0.6	0.1
Thiocyanate adjusted quit rate	31.0	19.2	11.8	36.1	22.2	13.9	−2.1
Change in diastolic BP (mm Hg)	−9.0	−5.0	−4.0	−10.4	−5.8	−4.6	0.6
% prescribed antihypertensive drugs	55.1	38.4	16.7	60.0	48.2	11.8	4.9
% prescribed ≤50 mg chlorthalidone	8.5	2.9	5.6	10.0	3.5	6.5	−0.9
% prescribed >50 mg chlorthalidone	10.5	1.1	9.4	10.8	1.4	9.4	0.0
% prescribed ≤50 mg hydrochlorothiazide	15.7	20.1	−4.4	18.8	27.1	−8.3	3.9
% prescribed >50 mg hydrochlorothiazide	15.1	2.9	12.2	13.9	3.7	10.2	2.0
% prescribed reserpine	13.7	4.6	9.1	13.3	5.7	7.6	1.5
% prescribed methyldopa	5.4	6.2	−0.8	6.7	8.0	−1.3	0.5
% prescribed propranolol	10.3	5.0	5.3	13.9	7.1	6.8	−1.5
% prescribed hydralazine	6.7	3.0	3.7	7.5	4.5	3.0	0.7
Serum potassium change (mEq/l)	−0.3	−0.1	−0.2	−0.3	−0.1	−0.2	0.0

* None of these differences are statistically significant.
BP = blood pressure; ECG = electrocardiogram; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SI = special intervention; UC = usual care.

or demonstrate different risk factor responses relative to similar men in the UC group than the men in the SI group with a normal exercise electrocardiographic response? Table VII displays risk factor changes and treatment characteristics of the 2 groups at 48 months by exercise electrocardiographic response. SI-UC differences for these multiple characteristics did not vary significantly by presence or absence of ischemia on the ECG.

Discussion

There were 3 main findings from these analyses. First, there was a substantial prevalence (12.5%) of an abnormal response to a heart-rate-limited exercise test using the computer-measured ST depression integral, despite having excluded men with evidence for overt CAD. Second, the abnormal response was highly predictive of CAD mortality in the UC group, with an adjusted relative risk of 3.44. Third, contrary to the hypothesis that the program would be especially beneficial in participants with a normal exercise ECG, no significant SI-UC difference in CAD mortality was found in this subgroup. However, among men with an abnormal exercise test a 57% lower rate of CAD mortality was observed in the SI compared with the UC group.

There were also unexpected findings related to the other subgroup hypothesis based on the ECG at rest, discussed in a separate report.[2] In the subgroup with normal baseline ECGs at rest, the SI group had a lower CAD mortality rate than the UC group, although the difference was not significant. In contrast, men in the SI group with abnormal ECGs at rest had a tendency toward a higher CAD mortality rate than their UC counterparts. This indication of a possible unfavorable outcome of the intervention program in the presence of an abnormal electrocardiographic response at rest was limited to men who were hypertensive at entry, in whom SI men had CAD mortality 65% higher than UC men.

These subgroup observations appear to be difficult to reconcile. However, the favorable response (SI vs UC) of abnormal exercise responders was independent of the unfavorable influence of an abnormal electrocardio-

graphic response at rest (Table VI). Apparently, there is a systematic difference in CAD death rates between the SI and UC group in favor of the SI among men with an abnormal response to exercise. For CAD mortality, this difference is, to a certain degree, attenuated by the presence of ECG abnormalities at rest; for all-cause mortality, it is eliminated.

An abnormal electrocardiographic response to exercise was associated with advanced CAD in many studies of symptomatic patients and asymptomatic men.[10,11] Prevalence of abnormal tests varies as much as 40-fold, depending on age, sex, presence or absence of symptoms, definition of a positive exercise electrocardiographic response, and exercise protocol used.[10–13] No 2 studies are exactly comparable, so that the prevalence of abnormal exercise response based on the electrocardiographic criteria used in MRFIT cannot readily be compared with the findings of other studies.

The criteria used in this study for an abnormal ECG response to exercise differ from the conventional clinical electrocardiographic criteria for an ischemic response which require a horizontal or downsloping ST segment depressed from the J point by 0.1 mV or more. The ST-depression integral measures the ST-segment area under the PR baseline and classifies the response as abnormal whenever the estimated upper normal limits for the integral are exceeded, irrespective of the slope of the ST segment.[14]

The use of such a computer-read negative ST-segment voltage-time integral as a measure of abnormal ECG response to exercise was first suggested by Sheffield et al.[15] They used the measurement to discriminate between normal persons and patients with angina pectoris. A later study[16] indicated that with an increasing value for the negative ST-segment voltage-time integral after exercise, there is a graded increase in CAD as measured angiographically. In the present study a similar graded risk of CAD death during a 7-year period was found as the negative ST-segment voltage-time integral at maximal exercise increased among both groups. White middle-aged men in the Lipid Research Clinics Follow-up Study with a positive exercise tolerance test response (visual or computer coding, or both) had a 5 to 8 times higher CAD mortality rate than men who did not have a positive test response.[17] The independent predictive value of the positive exercise test response among MRFIT participants is analyzed in more detail in another report (submitted for publication).

Reduction of the CAD risk factors—cigarette smoking, elevated serum cholesterol, elevated blood pressure, and obesity—among men with ischemic changes noted in their ECG at rest by the Minnesota code criteria in another study[18] resulted in a significant reduction in 6-year CAD incidence and total mortality compared to a group of similar controls not receiving intervention. In that same study there was no significant difference in 6-year CAD incidence among men without ischemic electrocardiographic changes at baseline between the intervention and the control group. Therefore, at least over a period of 6 years, benefit from risk factor reduction in middle-aged men is likely to be greater among those symptom-free men with ischemia revealed by the ECG than in those without this finding. This interpretation does not address the value of an early population-wide primary prevention strategy.

A possible explanation of the lack of significant difference in CAD rates between UC and SI groups among normal responders on both rest and exercise ECGs could be low statistical power. As illustrated by the observed confidence interval, any effect of intervention would be unlikely to be observed in a sample of this size among men with lesser degrees of coronary atherosclerosis at baseline, and therefore at low risk of CAD death.

The nature of the benefit among the abnormal exercise responders in MRFIT is reflected by an excessive number of sudden deaths in the UC compared to the SI group. The greater risk factor reduction may have resulted in a diminution or lesser progression of the atherosclerotic process in men in the SI group compared with those in the UC group. This could have prevented some sudden deaths; the incidence of sudden death increases sharply with increasing severity of CAD. Acute pathophysiologic consequences of coronary narrowing may also have been reduced, for example by the greater smoking cessation in the SI group. Such questions regarding mechanisms may be clarified by planned analyses of CAD morbid events, i.e., nonfatal myocardial infarction and angina pectoris.

Is there any insight that can be gained from the contrast between the apparent benefit from risk factor intervention in those with an ischemic-type electrocardiographic response to exercise, and the suggestion of an adverse effect in men with electrocardiographic abnormalities at rest? The pathophysiology that underlies electrocardiographic abnormalities during exercise is different from that of electrocardiographic abnormalities at rest. The latter may be more strongly related to cardiac muscle changes associated with hypertension, while the electrocardiographic changes noted in abnormal exercise response are more strongly related to ischemia. Further analyses of other CAD risk factor intervention studies may help to clarify these issues, and additional trials may be necessary.

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Appendix

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The principal investigators and senior staff of the clinical, coordinating, and support centers, the National Heart, Lung, and Blood Institute, and members of the MRFIT Policy Advisory Board and Mortality Review Committee are:

American Health Foundation, New York: Charles Arnold, MD, MPH (principal investigator), Rebecca Mandriota, MS, MEd, Richard Ames, MD, Joan Ruff Eisenbach, RN.

Boston University, Boston: H. Emerson Thomas, Jr, MD (principal investigator), William Kannel, MD (co-principal investigator), L. Kent Smith, MD, Charles Deckman.

Cox Heart Institute, Kettering, Ohio: Paul Kezdi, MD (principal investigator), Edwin Stanley, MD (co-principal investigator), Frederick Ernst, PhD, E. Jean Case, RN, MS.

Dade County Department of Public Health, Miami: George Christakis, MD, MPH (principal investigator), Janice Burr, MD (co-principal investigator), Terence Gerace, PhD (co-principal investigator), Mary Ellen Wilcox, RD, MEd.

Dalhousie University Halifax, Nova Scotia (MRFIT ECG Center): Pentti Rautaharju, MD, PhD (principal investigator), Hermann Wolf, PhD.

Harvard University, Boston: Robert Benfari, PhD (principal investigator), Kevin McIntyre, MD, JD (co-principal investigator), Oglesby Paul, MD (co-principal investigator; former chairperson, Steering Committee), Elinor Danielson, MA, Judith Ockene, PhD.

Kaiser Foundation Research Institute, Portland, Oregon: John Wild, MD (principal investigator), M. R. Greenlick, PhD (co-principal investigator), John Grover, MD (co-principal investigator), Sara Lamb, Jeffry Bailey, Judith Dyer, MSHyg, RD, Barbara Brokop, RN, Victor Stevens, PhD, Geraldine Bailey, RN.

Lankenau Hospital, Philadelphia: William Holmes, PhD (principal investigator), J. Edward Pickering, MD (co-principal investigator), James Allaire, MEd, Diane Fellon, RN, Barbara Feinstein, MSA, Diana Hutchins, MD.

National Center for Disease Control, Atlanta: Gerald Cooper, PhD, MD (principal investigator).

New Jersey Medical School, Newark: Norman Lasser, MD, PhD (principal investigator), Norman Hymowitz, PhD (co-principal investigator).

Northwestern University, Chicago: Jeremiah Stamler, MD (principal investigator), Dorothy Moss, MS, RD, Victoria Persky, MD, Linda Van Horn, PhD, RD, Kay Shannon, MA, David Meyers, MD.

University of Chicago, Chicago: Louis Cohen, MD (principal investigator), Juliet Morgan, PhD (co-principal investigator), Gayle Grundmann, MS, RD, Thomas Vestal, PA, Ben Huang.

St. Joseph's Hospital, Chicago: David Berkson, MD (principal investigator), Gary Lauger, MS, Stevan Grujic, MD, David Obradovic, MD.

Institutes of Medical Sciences–University of California, San Francisco and Berkeley: James Billings, PhD, MPH (principal investigator), Stephen Hulley, MD, MPH (co-principal investigator), W. McFate Smith, MD, MPH (co-principal investigator), S. Leonard Syme, PhD (co-principal investigator), Richard Cohen, MS, Lisa Dzvonik, MA, RD, Leslie Roos, Mary Kahn, RN.

Institutes of Medical Sciences, San Francisco Central Laboratory: Graham Widdowson, PhD (co-principal investigator), George Williams, MD (co-principal investigator), Stephen Hulley, MD, MPH (co-principal investigator).

Rush-Presbyterian-St. Luke's Medical Center, Chicago: James Schoenberger, MD (principal investigator), Joseph Schoenenberg, PhD, Richard Shekelle, PhD, Gilberto Neri, MD, Therese Dolecek, PhD, RD.

Rutgers Medical School, Piscataway, New Jersey: Nicholas Wright, MD, MPH (principal investigator), Steven Kopel, PhD (co-principal investigator), Kenneth Suckerman, PhD, Marilyn Schorin, MPH, RD.

St. Louis Heart Association, St. Louis: Nathan Simon, MD (principal investigator), Jerome Cohen, MD (co-principal investigator), Elizabeth Bunkers, RD.

University of Alabama in Birmingham: Harold Schnaper, MD (principal investigator), Glenn Hughes, PhD (co-principal investigator), Ralph Allen, PA, Phillip Johnson.

University of California, Davis: Nemat Borhani, MD (principal investigator), Carolyn Sugars, RD, Karen Kirkpatrick, Marshall Lee, MD, Frances LaBaw, RN.

University of Maryland, Baltimore: Roger Sherwin, MB, BChir (principal investigator), Mary McDill Sexton, PhD, MPH (co-principal investigator), Quely de Barros, MS, Patricia Dischinger, PhD, Jutta Heiner, MD, Mary Pilkington, RN, MSN, Barbara Scanlon, MA.

University of Minnesota, Minneapolis: Richard Grimm, Jr, MD, MPH (principal investigator), Henry Blackburn, MD (co-principal investigator), Richard Crow, MD (co-principal investigator), Maurice Mittelmark, PhD (co-principal investigator), Mary McDonald, RN, MS.

University of Minnesota ECG Coding Center, Minneapolis: Ronald Prineas, MB, PhD (director), Richard Crow, MD (associate director).

University of Minnesota Nutrition Coding Center, Minneapolis: Ida Buzzard, PhD (director), Joyce Wenz, MS, RD (associate director).

University of Minnesota Coordinating Center, Minneapolis: Marcus Kjelsberg, PhD (principal investigator), Glenn Bartsch, ScD (co-principal investigator), James Neaton, PhD (co-principal investigator), Steven Broste, MS, John Connett, PhD, Alain DuChene, Diane Gorder, MS, Gregory Grandits, MS, Kenneth Svendsen, MS.

University of Pittsburgh, Pittsburgh: Lewis Kuller, MD,

DPH (principal investigator), Robert McDonald, MD (co-principal investigator), Lorita Falvo-Gerard, MN, MPH (co-principal investigator), Arlene Caggiula, PhD, RD (co-principal investigator), Elizabeth Gahagan, RN, Roberta Moyer, RN, Mary Alman, RN, Karen Southwick, ASCP.

University of South Carolina, Columbia: Warren Giese, PhD (principal investigator), J. Frank Martin, MD (co-principal investigator), James Keith, PhD (co-principal investigator), Harriet Harrison, RN.

University of Southern California, Los Angeles: Eugene Fishman, MD (principal investigator), Laurence Wampler, PhD, Gretchen Newmark, MA, RD, Shahida Siddiqui, MD, Lauren Paquet, RN.

Policy Advisory Board: William Insull, Jr, MD (chairperson), John Farquhar, MD, C. David Jenkins, PhD, Elliot Rapaport, MD, Donovan Thompson, PhD, Herman Tyroler, MD, Park Willis III, MD, William Friedewald, MD (ex officio), William Zukel, MD (ex officio).

Mortality Review Committee: Joseph Doyle, MD (chairman), Howard Burchell, MD, Paul Yu, MD, Park Willis III, MD (former member).

National Heart, Lung, and Blood Institute Staff, Bethesda, Maryland: William Friedewald, MD (program director), Curt Furberg, MD (project office director), Jeffrey Cutler, MD (scientific project officer), William Zukel, MD (former program director), Eugene Passamani, MD (former scientific project officer), Charles Kaelber, MD (former scientific project officer), Joel Verter, PhD, Margaret Wu, PhD.

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Relation of Antianginal Efficacy of Nifedipine to Degree of Coronary Arterial Narrowing and to Presence of Coronary Collateral Vessels

WOLFGANG SCHULZ, MD, STEFAN JOST, MD, GISBERT KOBER, MD, and MARTIN KALTENBACH, MD

Thirty-six patients with chronic stable angina pectoris or with stable and vasospastic components of angina pectoris were classified by coronary arteriographic findings into 4 groups. Patients in group A had a single stenotic coronary artery; patients in groups B, C and D had occluded arteries, but these arteries had been collateralized to varying degrees, and an epicardial coronary steal phenomenon was possible. All patients underwent multiple exercise tests before and after randomized, double-blind, crossover treatment with 20 mg of nifedipine, 20 mg of isosorbide dinitrate, a combination of both, and placebo. Maximal and mean ST-segment depression, occurrence of angina pectoris and heart rate were evaluated. After nifedipine treatment, mean ischemic ST-segment depression was reduced 21% in group A ($p < 0.05$), but was not significantly altered in the other groups (group B, 2% decrease; group C, 10% increase; group D, 3% decrease). However, isosorbide dinitrate reduced ST-segment depression significantly in all groups (group A, 29%, $p < 0.001$; group B, 18%, $p < 0.01$; group C, 19%, $p < 0.05$; group D, 33%, $p < 0.05$). The combination with nifedipine did not further improve the effect of isosorbide dinitrate. Maximal ST-segment depression and angina pectoris paralleled the changes in mean ST depression during the different medications. Heart rate at rest was not significantly changed after nifedipine treatment in any group, but increased significantly after isosorbide dinitrate treatment in groups B and C (group B, 12%, $p < 0.01$; group C, 9%, $p < 0.05$); heart rate during exercise did not differ significantly in any group or after any form of medication from placebo. Thus, nifedipine fails to relieve myocardial ischemia if occluded but collateralized coronary arteries are present, indicating that the antianginal effect of this drug is influenced by underlying coronary pathomorphologic characteristics.

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The antianginal potency of calcium channel blockers has been the subject of many studies and is generally accepted.[1–3] However, the reduction of angina pectoris and ischemic ST-segment depression vary greatly.[4] In some studies, some patients have not responded at all to nifedipine treatment, and this was mainly attributed to a reflex tachycardia resulting from a decrease in systemic blood pressure.[2,5,6] However, tachycardia is not present in all nonresponders.[4]

Some pharmacologists have reported that nifedipine can induce a "steal phenomenon" due to a malignant vasodilation[7–11]; others consider nifedipine to be a benign vasodilator.[12,13] An increase in flow to areas supplied by normal or stenotic coronary arteries is generally accepted. However, in compromised myocardium supplied only by collaterals, the flow alterations remain unclear. An increased flow at rest has been described and was attributed to a better collateral blood flow.[14] Theoretically, however, an impaired collateral flow may also be assumed, because a coronary steal phenomenon predominantly occurs, if a major coronary artery is occluded and the depending myocardium is collateralized.[15]

In the present study we assessed whether the response to nifedipine is related to coronary anatomy.

Methods

Thirty-six patients with angiographically documented coronary artery disease without transmural myocardial infarction, myocardial aneurysm or heart failure were classified according to their coronary anatomy (Fig. 1): *group A*—patients with 1 stenotic artery (at least 70% diameter reduction) in the left anterior descending, left circumflex or right coronary artery; *group B*—patients with 1 occluded artery collateralized by another artery without a diameter reduction of

From the Zentrum der Inneren Medizin, Abteilung für Kardiologie, Klinikum der Johann Wolfgang Goethe, Universität Frankfurt/Main, Federal Republic of W Germany. Manuscript received June 18, 1984; revised manuscript received September 12, 1984, accepted September 13, 1984.

Address for reprints: Martin Kaltenbach, MD, Abteilung für Kardiologie, Zentrum der Inneren Medizin, Klinikum der J.-W.-Goethe Universität, Theodor-Stern-Kai 7, 6000 Frankfurt/Main, Federal Republic of Germany.

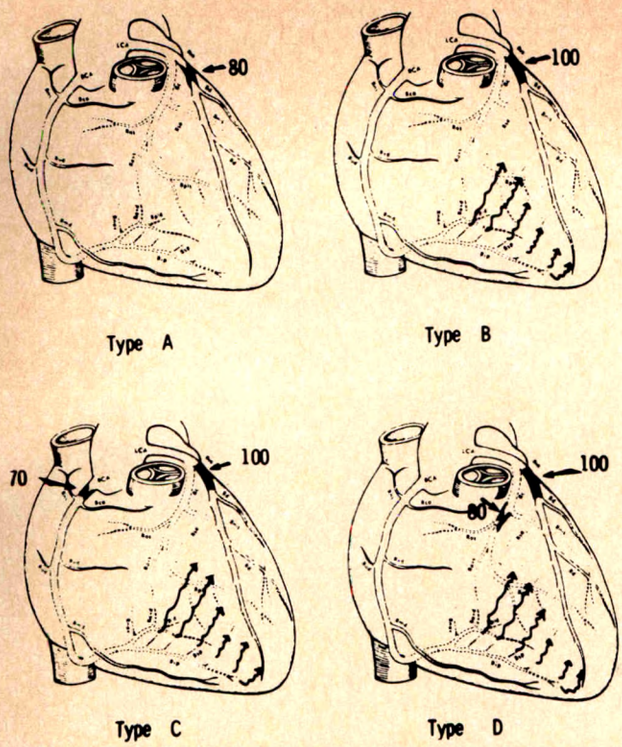

FIGURE 1. Coronary pathomorphologic characteristics of patients in groups A, B, C and D.

more than 50%; *group C*—patients with 1 occluded artery collateralized by another coronary artery with a proximal obstruction of more than 60%; and *group D*—patients with 1 occluded artery collateralized by another coronary artery without significant stenoses (less than 50%), but with a stenosis of more than 70% diameter reduction in the third major coronary artery branch.

Coronary pathomorphologic characteristics, age, sex and applied workload are listed in Table I. The degree of coronary narrowing was taken as the average diameter reduction as seen from 2 or more projections after vasodilatation with 1.6 mg of nitroglycerin sublingually.

In all patients, an ischemic ST-segment depression of 2 mm or more could be induced by an individually adjusted workload in physical exercise tests; subsequently, the reproducibility of ST-segment depression was assured in 2 control tests with this workload. Angina pectoris during exercise testing was present in 67% of the patients. In addition, all patients were carefully questioned about anginal symptoms at rest, indicating a possible additional vasospastic component (Table II). These occasional symptoms at rest are a finding in many patients with coronary artery disease. However, they did not influence the reproducibility of anginal threshold and ST-segment depression during repeated exercise tests.

Patients were randomly assigned in a double-blind, crossover fashion with double-dummy technique to the following regimens: 20 mg of nifedipine, 20 mg of isosorbide dinitrate, a combination of 20 mg of nifedipine and 20 mg of isosorbide dinitrate, and placebo.

Regular antianginal therapy was discontinued 48 hours before the beginning of the study. As β-blocking drugs were not part of the regular antianginal therapy, a rebound was not expected. Only sublingual nitroglycerin was allowed for acute episodes of angina.

The exercise tests were performed 60 minutes after oral administration of the medications; in each patient the tests

TABLE I Age, Sex, Coronary Pathomorphologic Characteristics and Workload of Patients in the 4 Groups

Pt	Age (yr)	Coronary Angiographic Diameter Reduction (%) LAD	LC	R	Workload (W)
		Group A			
1	57	90	0	0	55
11	57	80	0	20	140
12	63	70	20	0	190
15	58	0	30	90	195
17	54	80	0	0	55
18	54	80	0	0	100
20	50	95	40	30	110
21	55	90	0	0	85
24	55	0	80	0	80
26	57	0	0	80	140
29	52	80	0	0	155
Mean	56				139
±SD	3				49
		Group B			
2	59	30	40	100	170
4	47	0	0	100	160
9	67	100	0	0	135
13	49	0	0	100	135
14	65	35	40	100	165
32	40	20	100	0	215
33	47	0	40	100	220
34	57	10	0	100	145
35	73	100	10	40	110
36	48	30	100	20	160
Mean	55				162
±SD	11				35
		Group C			
3	54	90	0	100	140
5	62	100	30	70	125
7	63	50	100	90	165
10	53	90	40	100	85
22	37	80	0	100	150
23	50	70	100	80	175
25	54	60	50	100	135
27	36	95	60	100	160
30	58	60	40	100	140
31	54	60	99	100	205
Mean	52				148
±SD	9				32
		Group D			
6	50	40	100	65	195
8	62	100	80	40	80
16	51	95	0	100	115
19	53	90	100	40	75
28	53	80	30	100	155
Mean	54				124
±SD	5				51

LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; R = right coronary artery; SD = standard deviation.

were performed at the same time of day on 4 consecutive days according to the Kaltenbach protocol.[3] Workload and duration of exercise were kept constant during all 4 exercise tests in each subject. The ST-segment depression was manually measured and averaged out of 5 consecutive beats at each minute in leads V_4, V_5, V_6, I, II and III. The maximal ST-segment depression was determined, as was mean ST-segment depression, defined as average of ST depression during all minutes of exercise and 5 minutes of recovery. The onset and duration of angina pectoris (AP) were documented. Heart rate was averaged from 5 consecutive beats at the end of every minute during and after exercise. Statistical analysis was performed using Friedman's test and the subsequent analysis according to Wilcoxon and Wilcox.

TABLE II Results of a Questionnaire Regarding Symptoms Indicating the Variant Form of Angina in Group A, B, C and D

Angina Pectoris Occurring at Rest	Group A (n = 11)	Group B (n = 10)	Group C (n = 10)	Group D (n = 5)
Without special event	3	7	1	4
Cold	7	4	5	4
Weather change	9	5	6	2
Emotional stress	7	7	7	3

Results

ST-segment depression: The severity of ischemic ST-segment depression showed significant differences among groups A, B, C and D after nifedipine administration, whereas after isosorbide dinitrate no significant differences were seen. Maximal levels of ST-segment depression are listed in Table III; maximal levels of ST-segment depression during exercise with each regimen are shown in Figure 2; mean levels of ST-segment depression are listed in Figure 3.

Nifedipine: In group A, 20 mg of nifedipine reduced mean and maximal ST-segment depression by 21% ($p < 0.05$) and 26% ($p < 0.05$), respectively. In group B, nifedipine reduced mean and maximal ischemic ST-segment depression by 2% (difference not significant [NS]) and 5% (NS)—a response similar to that during placebo treatment. In group C, in contrast, nifedipine increased mean and maximal ischemic ST-segment depression by 10% (NS) and 12% (NS), respectively. In group D, no significant changes of mean and maximal ST-segment depression were noted (decrease of 3% and increase of 5%, respectively).

Isosorbide dinitrate: Isosorbide dinitrate, 20 mg, diminished mean ST-segment depression in group A by 29% ($p < 0.001$), in group B by 18% ($p < 0.01$), in group C by 19% ($p < 0.05$), and in group D by 33% ($p < 0.05$).

Nifedipine and isosorbide dinitrate combined: The mean decreases in ST-segment depression after the combination were not significantly different from those during isosorbide dinitrate alone: group A, 34%; group B, 19%; group C, 24%; group D, 19%.

After treatment with isosorbide dinitrate or the combination of nifedipine with isosorbide dinitrate, the changes in maximal ST-segment depression paralleled the changes in mean ST-segment depression.

Angina pectoris: As a subjective measure of myocardial ischemia, the time of onset, the sum of all minutes with AP during and after exercise and the patients without AP were counted (Table IV). After nifedipine treatment, in group A, AP had a later onset and decreased duration; 1 patient who had AP after placebo did not show angina after nifedipine. In groups B, C and D, however, AP occurred slightly earlier and the duration was prolonged; 1 patient in group C who did not have AP after placebo had it after nifedipine. After isosorbide dinitrate treatment, AP occurred later or not at all in the groups A, C and D, and the duration decreased slightly. The effects of the combination were comparable to those after isosorbide dinitrate treatment alone.

TABLE III Maximal ST-Segment Depression During Exercise Testing After Nifedipine, Isosorbide Dinitrate, a Combination of Nifedipine and Isosorbide Dinitrate, and Placebo

	Maximal ST-Segment Depression (mm)			
Pt	Placebo	N	ISDN	N + ISDN
		Group A		
1	5	2	4.4	1
11	2.3	1.2	1.2	1.2
12	2	2.4	1.5	1.6
15	1.6	1	1.3	1.7
17	2	1	0.7	0.8
18	1.9	1.4	1.2	1.3
20	2.3	2	1.2	1.7
21	2.5	2.5	1.1	1.2
24	2.1	2	1.7	2
26	3.2	2.5	2	2.2
29	3.2	2.9	1.5	1.8
Mean	2.6	1.9	1.6	1.5
±SD	1	0.7	1	0.4
p		<0.05	<0.001	<0.01
		Group B		
2	3	3	2.7	3
4	3	3	1.5	2
9	3	3.2	2.7	2.6
13	1.3	1.2	1.4	1
14	2	1.5	1.4	1.5
32	2.1	1.6	1.6	1.5
33	1.5	2.5	2	1.5
34	2.5	2.1	2.7	1.9
35	2.6	2	2.1	2
36	3.4	3.2	2.6	3
Mean	2.4	2.3	2.1	2
±SD	0.7	0.8	0.6	0.7
p		NS	<0.01	<0.01
		Group C		
3	4.5	4.3	4.5	4
5	1.7	2.3	3	2
7	3.5	4.1	2.5	2.5
10	4	4	3.4	3.6
22	3.5	3.5	2.5	2.2
23	1.8	2	2	2.2
25	3	4.1	1.6	1.6
27	2	2	2	1.7
30	2.5	3.2	2.3	2.6
31	2.1	2.6	2	2
Mean	2.9	3.2	2.6	2.4
±SD	1	0.9	0.9	0.8
p		NS	<0.05	<0.05
		Group D		
6	1.8	1.8	1.5	0.7
8	4.7	4.7	3.5	4.5
16	3	3	2.3	2
19	1.8	3	1.2	1.6
28	3.5	3	1.7	2.7
Mean	3	3.1	2	2.3
±SD	1.2	1	0.9	1.4
p		NS	<0.05	<0.05

ISDN = isosorbide dinitrate; N = nifedipine; NS = not significant; SD = standard deviation.

Heart rate: The mean heart rate at rest and during and after exercise is shown in Figure 4. Heart rates at rest were slightly higher in the treatment groups; these values were not significantly different from placebo except after isosorbide dinitrate treatment in group B and C (group B, 12% increase, $p < 0.01$; group C, 9% increase, $p < 0.05$). During exercise, no significant changes in heart rate were noted. During nifedipine treatment neither a reflex tachycardia at rest nor a higher increase

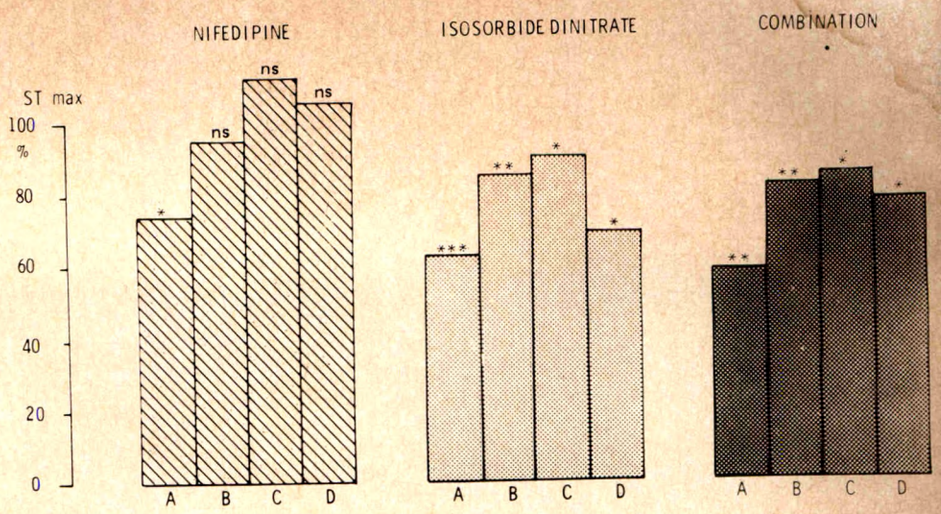

FIGURE 2. Maximal ST-segment depression during exercise tests after treatment with different medications in the 4 groups compared to placebo. ns = not significant.

in heart rate during exercise was noted in any patient in group B, C or D.

Discussion

Conflicting results concerning the antianginal potency of nifedipine have been reported. A higher exertional ST-segment depression was reported by Loos and Kaltenbach[1] in 1 of 18 patients, Becker et al[5] in 2 of 11 and Kober et al[2] in 2 of 10 patients; an exacerbation of anginal symptoms was reported by Stone et al[6] in 100 of 716 patients. In our clinical experience, nifedipine fails to relieve exertional angina in 10 to 20% of the patients. This was partially ascribed to a reflex tachycardia due to a decrease in systemic blood pressure. However, Fox et al[4] reported about nonresponders to nifedipine therapy without important changes in heart rate. The present study confirms these observations. We examined whether there is evidence for a "coronary steal" phenomenon as the cause for the lack of response to nifedipine.

Fam and McGregor[16] and Schaper et al[17] described a myocardial steal phenomenon after application of an arteriolar vasodilator (dipyridamole) that is induced by inhibition of coronary arteriolar autoregulation. This reduction in coronary resistance may induce myocardial ischemia by directing flow from an underperfused area to normally perfused myocardium. McGregor[18] stated

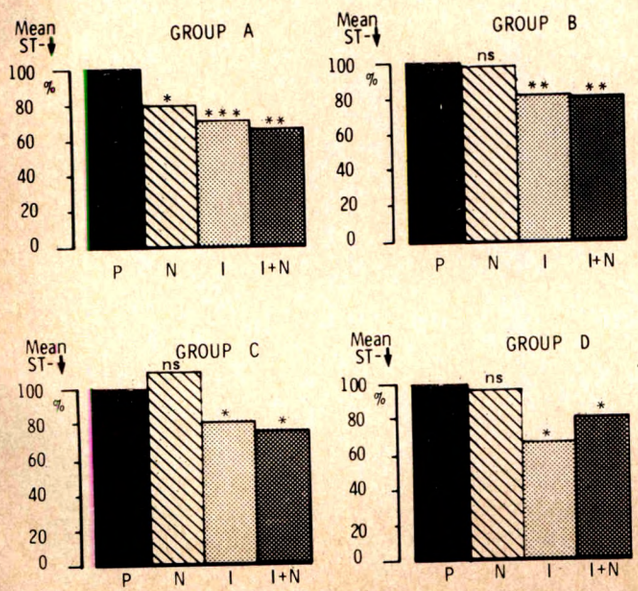

FIGURE 3. Mean ST-segment depression in exercise tests after treatment with nifedipine (N), isosorbide dinitrate (I), combination (I + N) and placebo (P).

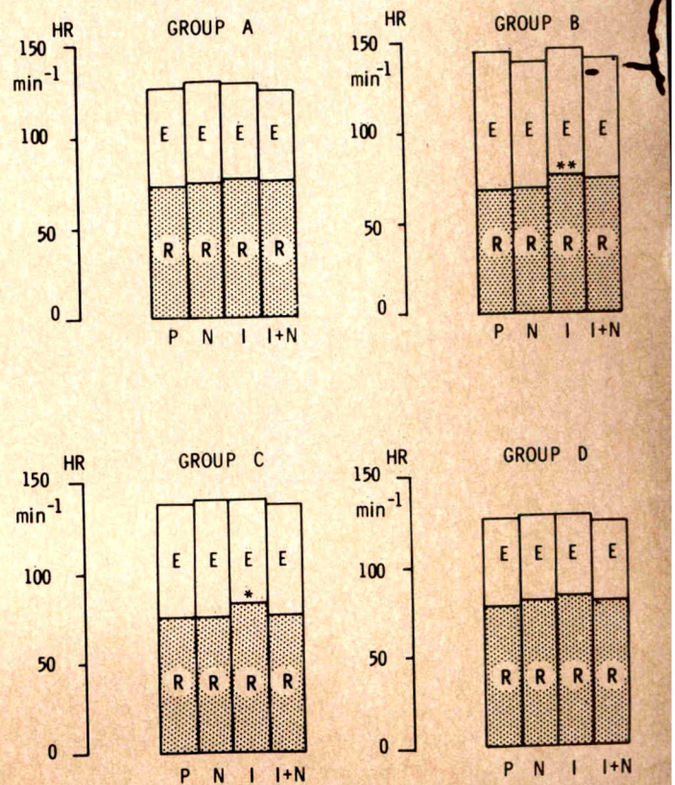

FIGURE 4. Heart rate (HR) at rest (R) and exercise (E) after treatment with nifedipine (N), isosorbide dinitrate (I), combination (I + N), and placebo (P). *p <0.05, 2-tailed.

TABLE IV Onset of Angina Pectoris and Sum of Minutes with Angina Pectoris in the Exercise Tests After Administration of Nifedipine, Isosorbide Dinitrate, Combination of Nifedipine and Isosorbide Dinitrate, and Placebo

	Onset (O) and Sum (S) of Angina (AP) During and After Exercise (minutes)							
	Placebo		N		ISDN		N + ISDN	
Pt	O	S	O	S	O	S	O	S
Group A								
1	3	3	4	2	2	4	—	0
11	4	3	—	0	—	0	—	0
12	—	0	—	0	—	0	—	0
15	—	0	—	0	—	0	—	0
17	—	0	—	0	—	0	—	0
18	3	7	3	5	3	5	3	5
20	2	6	2	8	—	0	—	0
21	2	2	2	2	—	0	—	0
24	2	2	2	3	2	2	2	4
26	2	4	2	3	3	2	3	1
29	4	4	4	4	4	3	5	2
Median of sum of AP	—	3	—	2	—	0	—	0
Pts without AP	3	—	4	—	6	—	7	—
Group B								
2	—	0	—	0	—	0	3	1
4	3	5	2	5	2	3	3	4
9	2	2	2	2	2	2	2	2
13	3	4	3	4	4	3	4	3
14	—	0	—	0	—	0	—	0
32	—	0	—	0	—	0	—	0
33	—	0	—	0	—	0	—	0
34	2	3	2	3	2	3	3	2
35	4	2	3	4	3	2	4	2
36	2	6	2	7	2	7	1	8
Median of sum of AP	—	2	—	2.5	—	2	—	2
Pts without AP	4	—	4	—	4	—	4	—
Group C								
3	4	2	4	2	4	2	4	2
5	3	2	3	2	3	2	3	1
7	—	0	—	0	—	0	—	0
10	—	0	5	3	5	1	5	1
22	—	0	—	0	—	0	—	0
23	3	2	3	6	3	2	2	4
25	2	3	2	4	—	0	4	1
27	5	3	5	3	—	0	5	2
30	2	3	2	4	3	2	2	3
31	—	0	—	0	—	0	—	0
Median of sum of AP	—	2	—	2.5	—	0.5	—	1
Pts without AP	4	—	3	—	5	—	3	—
Group D								
6	—	0	—	0	—	0	—	0
8	2	5	1	5	3	3	2	4
16	2	4	2	4	4	2	3	3
19	5	1	4	6	5	1	5	1
28	2	5	3	3	3	2	2	4
Median of sum of AP	—	3	—	4	—	2	—	3
Pts without AP	1	—	1	—	1	—	1	—

ISDN = isosorbide dinitrate; N = nifedipine.

that the coronary steal phenomenon "could, of course, only occur if the input was restricted" (Fig. 5). However, the precise conditions were controversial,[19,20] until Becker et al[15] demonstrated with dipyridamole treatment in dogs, that the coronary steal phenomenon occurs, if collateral vessels supply myocardium behind coronary occlusions and even more, if the collateral providing vessel is proximally stenotic.

An inhibition in metabolic autoregulation after nifedipine administration can also be assumed after intravenous or intracoronary injections, as judged by the increase in coronary flow[21] or coronary sinus oxygen saturation[22]; after sublingual application a smaller but longer-lasting increase of the coronary sinus oxygen saturation was found in dogs[12] as well as in humans.[8]

For this study, groups of patients with and without collateral vessels were selected. The hypothesis was that in patients without collateral vessels, nifedipine would be effective, whereas in patients with collateral vessels, a coronary steal phenomenon could diminish the antianginal efficacy of nifedipine.

The antianginal efficacy in patients without collateral vessels may be explained by dilatation of "dynamic" coronary stenoses. Significant widening of critical

stenoses has been shown by several investigators,[21–23] and a better oxygen supply improved the efficacy of nifedipine.[24]

Among patients in group B(as defined in Methods), a reduction of myocardial ischemia with significant reduction of AP or ST-segment depression was not seen. Antianginal mechanisms often cited to explain the efficacy of nifedipine are reduction of afterload, improved collateral flow or metabolic effects on the myocardium are not sufficient in group B patients to reduce myocardial ischemia.

Changes in afterload do not correspond well to the antianginal efficacy of nifedipine, and some paradoxical reactions have been described; the blood pressure during exercise may be even higher, when the antianginal effect is present, and even lower when nifedipine is ineffective.[21,24,25] In the present study, blood pressure was not measured and this may limit our conclusions. However, the blood pressure reaction to nifedipine was grossly uniform in patients who were normotensive. Some differences in blood pressure alone would hardly explain the ineffectiveness of nifedipine in the selected patients in groups B, C and D; 17 of 25 patients showed an unchanged or even worse maximal ST-segment depression. But the possibility cannot be excluded that a low blood pressure response aggravates the negative effects in patients prone to a steal phenomenon, as proposed by Hintze and Vatner.[26]

Improved collateral flow after nifedipine has been shown in dogs[27,28] after coronary ligation. During physical exercise in men, however, there was no improvement of ST-segment depression. Thus, an increase in collateral flow is apparently of no importance.

A metabolic effect on the myocardium was postulated to explain the antianginal efficacy of intracoronary nifedipine[29] and a metabolic effect has subsequently been proved.[21] In patients with coronary occlusions and collateral vessels, however, these possible beneficial effects on ischemia are overcome by the adverse effects of the coronary steal phenomenon.

If input is even more limited in patients in group C, 3 vascular effects may interfere after nifedipine therapy: dilation of epicardial coronary stenosis and dilation of epicardial collateral vessels are the favorable effects and dilation of metabolically regulated arterioles and capillaries in noncollateralized areas is an unfavorable effect. Dilation of stenoses or dilation of collaterals was apparently not sufficient to overcome the unfavorable effect of nifedipine on resistance vessels in these patients.

The lack of antianginal effect of nifedipine in patients in groups B, C and D cannot be related to an abnormal response in heart rate. After nifedipine, heart rates at rest and during exercise did not differ significantly in any group.

Results with the dipyridamole test in men confirm the validity of the above anatomic classification in regard to the possible induction of a steal phenomenon: A positive test can only be provoked if an occluded but collateralized coronary artery is present (manuscript in preparation).

All different forms of coronary pathomorphology can be found in patients with chronic stable angina or with additional "vasospastic symptoms" of angina pectoris. Seven of 10 patients in group B, 7 of 10 in group C and 4 of 5 in group D had symptoms indicating a vasospastic component of angina (Table II). Although it is generally assumed that nifedipine is especially effective in these patients,[30] it was not in patients with the coronary pathomorphologic characteristics of groups B, C and D. This finding again corresponds well to the clinical observation that nifedipine fails to relieve angina pectoris even in some patients with vasospastic components of angina.[6]

This study demonstrates the influence of coronary pathomorphology on the antianginal efficacy of nifedipine. For the first time, morphologic characteristics have been defined that influence the therapeutic efficacy of a calcium-blocking drug. The dependency on coronary anatomy may have important consequences in regard to antianginal therapy. Although in some patients dilation of coronary stenoses may be an important part of the antianginal efficacy of calcium-channel blocking agents, in other patients the occurrence of a steal phenomenon may diminish, abolish or even reverse its effect. It should be emphasized that the antianginal effect of nitrates, on the other hand, was preserved and grossly uniform in all 4 groups. Nitrates do not affect resistance vessels; they may dilate dynamic coronary stenoses and improve collateral flow by either direct or indirect mechanisms, especially by reducing preload variables.

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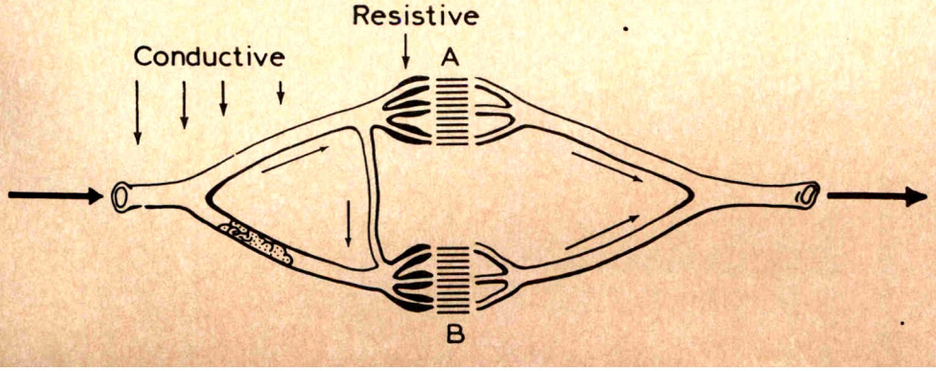

FIGURE 5. Schematic illustration of the steal phenomenon.[18] Dilation of "A" vessels induce increase in flow to normal perfused areas, with a further reduction in collateral perfused "B" vessels.

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Coronary Hemodynamic and Metabolic Effects of Nifedipine in Patients with Coronary Artery Disease Treated with Beta-Blocking Drugs

PETER SCHANZENBÄCHER, MD, GERHARD GÖTTFERT, MD, GERHART LIEBAU, MD, and KURT KOCHSIEK, MD

In humans, reflex sympathetic nerve activation modulates the direct cardiac action of nifedipine after systemic administration and results in a positive chronotropic and inotropic response. The coronary hemodynamic and metabolic effects of nifedipine were evaluated after propranolol-induced acute β-receptor blockade in 12 patients with angiographically documented coronary artery disease. The intravenous injection of propranolol led to a decrease in heart rate, coronary blood flow and myocardial oxygen consumption and an increase in coronary vascular resistance and the coronary arteriovenous oxygen difference. Mean aortic pressure did not change. The subsequent intravenous administration of nifedipine resulted in a transient increase in coronary blood flow and a reduction in coronary vascular resistance and the coronary arteriovenous oxygen difference and a sustained decrease in mean aortic pressure and myocardial oxygen consumption without significant changes in heart rate. Thus, in the presence of β-receptor blockade, the positive chronotropic response to nifedipine is attenuated and nifedipine reduces myocardial oxygen consumption significantly. The vasodilatory effect of nifedipine is maintained and a potential propranolol-related inappropriate vasoconstriction may be reversed. The combination of nifedipine and β-receptor blocking agents may be useful in the treatment of patients with both effort-induced angina and angina related to changes in coronary vasomotor tone.

(Am J Cardiol 1985;55:33–36)

The calcium channel blocker nifedipine is being used widely in the treatment of symptomatic coronary artery disease (CAD). Nifedipine has a negative inotropic effect on isolated heart muscle preparations and is a potent vasodilator of coronary arteries and other vessels.[1] In man, intravenous nifedipine therapy reduces left ventricular afterload and increases myocardial blood flow transiently.[2] However, after systemic administration, nifedipine does not decrease myocardial oxygen consumption significantly.[2,3] In humans, a negative inotropic and oxygen-saving effect of nifedipine is evident only after local application in the absence of peripheral hemodynamic effects.[2,4,5] The discrepancy between clinical and experimental data has been explained as the result of compensatory sympathetic activation counteracting the direct myocardial effects.

A recent experimental study suggested that the positive chronotropic and inotropic response to nifedipine could be modulated by autonomic blockade.[6] Clinically, nifedipine is frequently used in combination with β-blocking drugs.[7–9] However, no information is available regarding the effects of this combination on the coronary circulation of patients with CAD. In the present study, therefore, we evaluated the acute coronary hemodynamic and metabolic effects of nifedipine after β blockade by propranolol.

Methods

Patients: The study was performed in 12 patients, 11 men and 1 woman, who were undergoing routine cardiac catheterization for angina pectoris. CAD was defined as a 70% diameter reduction of 1 or more major coronary arteries. Patient data are summarized in Table I.

Catheterization: Each patient gave informed consent for the procedures described herein. Drug treatment was withheld

From the Department of Medicine, University of Würzburg, Würzburg, Federal Republic of Germany. This study was supported in part by Research Grant Scha 291/3-3 from Deutsche Forschungsgemeinschaft, Bonn, Federal Republic of Germany. Manuscript received April 9, 1984; revised manuscript received August 21, 1984, accepted September 4, 1984.

Address for reprints: Peter Schanzenbächer, MD, Department of Medicine, University of Würzburg, Josef-Schneider-Strasse 2, 8700 Würzburg, Federal Republic of Germany.

TABLE I Clinical and Diagnostic Data

Pt	Age (yr) & Sex	CI (l/min/m²)	LVEDP (mm Hg)	EF (%)	Coronary Angiography			Ventriculography
					R	LAD	LC	
M.A.	64M	4.3	14	64	−	−	+	Inf hyp
B.H.	48M	3.0	12	70	−	+	+	N
R.F.	53F	3.0	10	67	+	−	−	N
M.S.	52M	2.7	14	63	−	+	+	Inf hyp
W.R.	43M	2.0	9	55	−	+	+	Ant hyp
S.H.	50M	2.2	12	76	+	−	−	N
H.W.	53M	3.0	14	70	−	+	−	N
L.G.	40M	3.0	13	78	−	+	+	N
W.E.	55M	2.5	20	53	+	+	+	Diff hyp
K.E.	42M	2.7	10	80	−	+	−	N
J.R.	54M	2.7	10	80	+	−	−	N
K.D.	47M	2.7	12	70	−	+	+	N

Ant hyp = anterior hypokinesia; CI = cardiac index; Diff hyp = diffuse hypokinesia; EF = ejection fraction; Inf hyp = inferior hypokinesia; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; LVEDP = left ventricular end-diastolic pressure; N = normal; R = right coronary artery; + = >70% stenosis present; − = stenosis absent.

for 24 hours before study. Right- and left-sided cardiac catheterization, single-plane ventriculography, and selective coronary angiography in multiple projections were performed using the femoral route. A preshaped coronary sinus catheter with 2 thermistors and bipolar pacing electrodes (type CCS-7U-90B, Wilton Webster Laboratories) was inserted from the right antecubital vein and positioned in the mid-coronary sinus. When connected to the Wilton Webster 2-channel Wheatstone bridge and a chart recorder, it allowed measurements of the coronary sinus blood flow by the thermodilution method.[10,11] Catheter positions were frequently documented on videotape throughout the study so that a constant catheter position could be maintained.

Protocol: There was at least a 15-minute interval between the last injection of contrast medium for diagnostic coronary angiography and coronary sinus blood flow measurements. Coronary sinus blood flow (CSBF), myocardial oxygen consumption (MVO_2) heart rate and aortic pressure were determined at rest. Propranolol, 0.1 mg/kg, was injected at a rate of 1 mg/min. Heart rate and aortic pressure were continuously monitored. Ten minutes after the intravenous injection of propranolol, measurements were repeated. Thereafter, 1 mg of nifedipine in a 10-ml solution was continuously infused over 2-minutes. CSBF, MVO_2, heart rate and aortic pressure were measured immediately after the completion of the infusion and 5 and 15 minutes later. No side effects were observed during or after the propranolol and nifedipine infusions.

Measurements and calculations: Coronary sinus blood flow was measured by the constant-infusion thermodilution technique.[10,11] Coronary sinus blood flow measurements were performed during continuous infusion of 5% dextrose in water at room temperature with a constant infusion rate of 36 ml/min maintained by a Harvard pump. Arterial and coronary sinus blood samples were simultaneously drawn for determination of oxygen content. Oxygen content was measured using a Lex-O_2-Con-K (Lexington Instruments Corp.). MVO_2 was calculated from the product of the arteriovenous oxygen content difference and coronary sinus blood flow (CSBF): $MVO_2 = CSBF \times (A_0O_2 - CSO_2)$, where A_0O_2 = arterial oxygen content and CSO_2 = coronary venous oxygen content. Coronary vascular resistance (CVR) was derived from the ratio of mean aortic pressure (PA_0) to CSBF: $PA_0/CSBF$.

Data before and after propranolol and nifedipine injection were compared and evaluated by paired Student *t* test.

Results

After propranolol administration, heart rate decreased from 73 ± 14 to 66 ± 9 ($p < 0.025$). Mean aortic pressure did not change significantly (115 ± 21 vs 116 ± 19 mm Hg). CSBF decreased from 117 ± 27 to 104 ± 26 ml/min and MVO_2 from 15.7 ± 2.6 to 14.0 ± 2.8 ml O_2/min ($p < 0.001$). CVR increased from 1.01 ± 0.22 to 1.17 ± 0.28 mm Hg/ml/min ($p < 0.001$). The decrease in CSBF was accompanied by a moderate but statistically significant increase in the arteriovenous oxygen difference, from 13.2 ± 1.9 to 13.5 ± 1.8 vol% ($p < 0.01$).

The subsequent intravenous injection of 1 mg of nifedipine reduced the mean aortic pressure from 116 ± 19 to 97 ± 20 mm Hg ($p < 0.005$). Heart rate averaged 79 ± 9 and was not significantly different from values at rest ($p < 0.2$). CSBF increased to 148 ± 30 ml/min ($p < 0.001$) and CVR decreased to 0.66 ± 0.07 mm Hg/ml/min ($p < 0.001$). MVO_2 decreased to 12.9 ± 3.0 ml O_2/min ($p < 0.005$) and the arteriovenous oxygen difference was reduced to 8.7 ± 1.7 vol% ($p < 0.001$).

Five minutes after the nifedipine injection, heart rate (73 ± 7 beats/min), CSBF (113 ± 31 ml/min), CVR (0.97 ± 0.21 mm Hg/ml/min) and the arteriovenous oxygen difference (12.5 ± 2.0 vol%) were not different from control values. Mean aortic pressure (106 ± 19 mm Hg) and MVO_2 (13.7 ± 3.2 ml O_2/min) were significantly reduced at 5 minutes and 15 minutes after the injection (108 ± 16 mm Hg and 13.5 ± 3.2 ml O_2/min, $p < 0.005$). Tables II and III list the individual changes in CSBF and MVO_2. In all patients CSBF flow decreased after propranolol and increased transiently after nifedipine administration. MVO_2 was consistently lowered by propranolol, but the response to nifedipine treatment was more variable. Whereas 8 patients showed a decrease in MVO_2 after nifedipine, 4 patients showed a moderate increase 2 minutes after the injection. The latter 4 patients also showed a pronounced increase in heart rate.

Discussion

Coronary and metabolic effects of propranolol: Propranolol produced a significant reduction in MVO_2 and an increase in CVR. These effects have been reported previously.[12–14] However, other studies have suggested that no significant change in CSBF occurs.[15] Propranolol decreased left ventricular oxygen utilization in our patients. Thus, the decrease in CSBF ap-

TABLE II Changes in Coronary Sinus Blood Flow (ml/min) After Propranolol and Nifedipine Treatment

Pt	R	PR	N2	N5	N15
M.A.	114	110	138	118	108
B.H.	83	73	126	82	92
R.F.	92	88	120	96	96
M.S.	141	126	176	110	110
W.R.	81	63	90	63	63
S.H.	109	94	132	87	73
H.W.	132	120	154	125	127
L.G.	167	148	196	170	144
W.E.	93	78	137	136	78
K.E.	121	110	177	134	109
J.R.	150	139	184	150	134
K.D.	125	95	149	88	90
Mean	117	104	148	113	102
±SD	±29	±26†	±31†	±31	±25*

* $p < 0.01$; † $p < 0.001$.
N2, N5, N15 = 2, 5 and 15 minutes after the nifedipine injection; PR = propranolol; R = control value; SD = standard deviation.

TABLE III Changes in Myocardi (ml O_2/min) After Pr

Pt	R	PR	
M.A.	16.2	16.1	10.
B.H.	14.1	11.8	14.
R.F.	13.1	12.2	13.
M.S.	14.7	13.2	12.
W.R.	9.8	7.6	6.
S.H.	17.5	15.2	12.
H.W.	18.6	17.6	15.
L.G.	16.5	15.5	14.
W.E.	14.0	11.7	13.6
K.E.	18.2	16.2	18.7
J.R.	17.2	16.8	12.5
K.D.	18.1	14.1	10.3
Mean	15.7	14.0	12.9
±SD	±2.6	±2.8†	±

* $p < 0.025$; † $p < 0.001$.
Abbreviations as in Table II.

pears to be related primarily to reduced myocardial oxygen requirements. Decreases in cardiac index and left ventricular stroke work index, as well as reductions in indexes of left ventricular contractility, have been reported after propranolol administration.[16,17] These changes indicate reduced myocardial oxygen demand. Schang and Pepine[12] could not find significant propranolol-related changes in CSBF and MVO_2 when heart rate was maintained by atrial pacing. Their findings suggested that coronary vasoconstriction occurring after propranolol is predominantly an autoregulatory phenomenon.

However, in our patients we observed a moderate but significant increase in the arteriovenous oxygen difference after administration of propranolol. This increase in left ventricular oxygen extraction suggests that the propranolol-related increase in CVR is not a pure autoregulatory phenomenon and may indicate inappropriate vasoconstriction. Theoretically, acute blockade of vasodilatory β-adrenergic receptors may increase CVR by enhancing the α-adrenergic vasoconstrictor response. Orlick et al[18] reported important coronary arterial α-tonus at rest in patients with CAD, and exacerbation of angina pectoris by propranolol has been reported.[19]

A propranolol-related inappropriate vasoconstriction has been suggested by Wolfson and Gorlin,[14] but this finding was not confirmed by other investigators.[13,15,17] These conflicting results may be explained by differences in the distribution and density of α and β receptors in individual patients and differences in the sympathetic tone at rest. Pretreatment with β-blocking agents before the study may also be important. Changes in β-adrenergic receptor density in patients with heart failure during therapy has been reported.[20]

Coronary effects of nifedipine: In the presence of acute β-receptor blockade, nifedipine preserved its systemic and coronary arterial dilating effect. There was a marked and sustained decrease in mean aortic pressure and a pronounced but transient increase in CSBF. The increase in CSBF is in the range observed in patients without β-blocker treatment after intravenous administration.[2]

Because of the complex actio on coronary perfusion pressur poststenotic epicardial corona sistance, and intraluminal diste dividual patients may have a p nifedipine. We recently obser transient occlusion at the site of with associated angina pectoris ever, all patients showed an incr administration of nifedipine (T

The increase in CSBF was ac icant reduction in the arterioven This indicates temporary overper to basal levels within 5 minute ministration. Prolonged dilatio coronary arteries after nifedipir been documented; this implies t in a sustained relaxation of ep vessels, while intramural arteriol dilated.[2,5]

Metabolic effects of nifedipi acute β-receptor blockade by pr produced a significant and sus MVO_2. However, when nifedipine no detectable changes in MVO_2 h humans.[2,3] This is in contrast to studies.[1]

In conscious animals and in hu diac action of nifedipine appear modified by the systemic hypote receptor activation of autonomic re intravenous nifedipine consisten chronotropic and inotropic respons the positive chronotropic response attenuated, but not completely ab sistent with recent data in consci strumented animals.[6] Experimenta that because of its potential memb tion, propranolol may reduce baro

Thus, the decrease in MVO_2 a ministration appears to be relatec heart rate response and to the sus afterload resulting from systemic tionally, a decrease in left ventricu

formance may contribute to the reduction in MVO_2. A depression of left ventricular contractile performance as assessed by left ventricular dP/dt max after nifedipine has been reported in patients who receive chronic β-blocker therapy.[26]

Clinical implications: This study demonstrates that in patients with CAD, nifedipine reduces MVO_2 after pretreatment with propranolol (Table III). The coronary arterial vasodilatory effect of nifedipine is maintained in the presence of β-receptor blockade, and a probable propranolol-induced inappropriate vasoconstriction may be offset by nifedipine. The combination of nifedipine and propranolol may be useful in treating patients with effort-induced angina when symptoms cannot be controlled by monotherapy. In contrast to other calcium channel blockers, nifedipine combined with β-receptor blockers does not induce detrimental effects on sinus node and atrioventricular node function.[27] However, the combination should be used carefully, because adverse effects have been observed occasionally, especially in patients with left ventricular dysfunction.[28–30]

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Announces a major advance in the short-term management of heart failure

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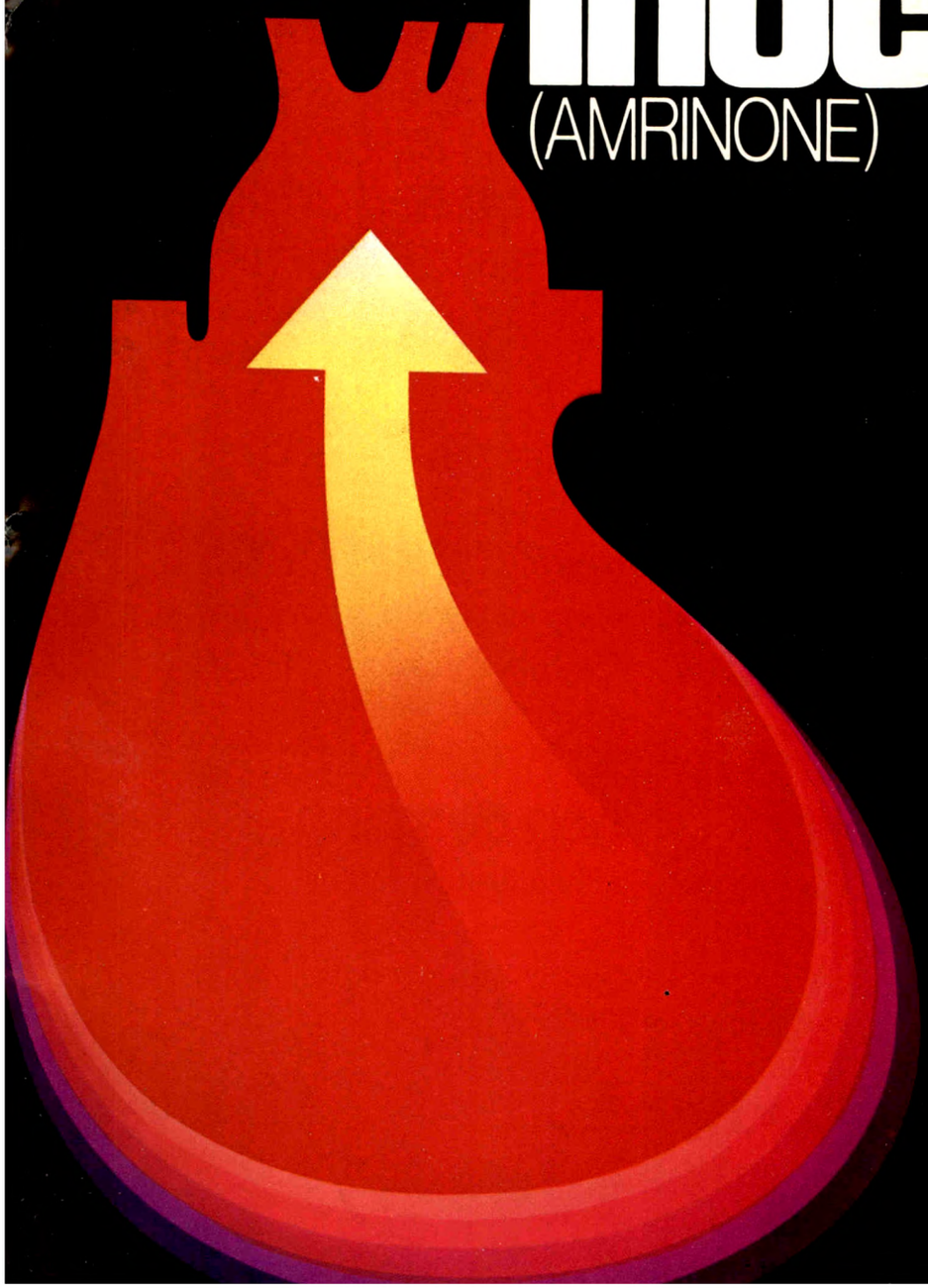

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INOCOR provides distinctive inotropic action for the short-term management of heart failure in patients who have not responded adequately to digitalis, diuretics, and/or vasodilators

distinctive inotropic action...

- Rapidly increases cardiac output and lowers filling pressure*
- No significant change in heart rate or blood pressure*
- Vasodilating action reduces the strain on the failing heart
- Symptomatic relief can be expected following hemodynamic improvement
- Independent of the effects of digitalis or catecholamines

rapidly stabilizes the failing heart without adding to myocardial oxygen demand

- Improves the efficiency of the failing heart because myocardial oxygen demand is usually unchanged
- Intended for use in patients who can be closely monitored and do not respond adequately to prior therapy*

heart rate and blood pressure not significantly changed

- Has not been shown to increase the risk of arrhythmias

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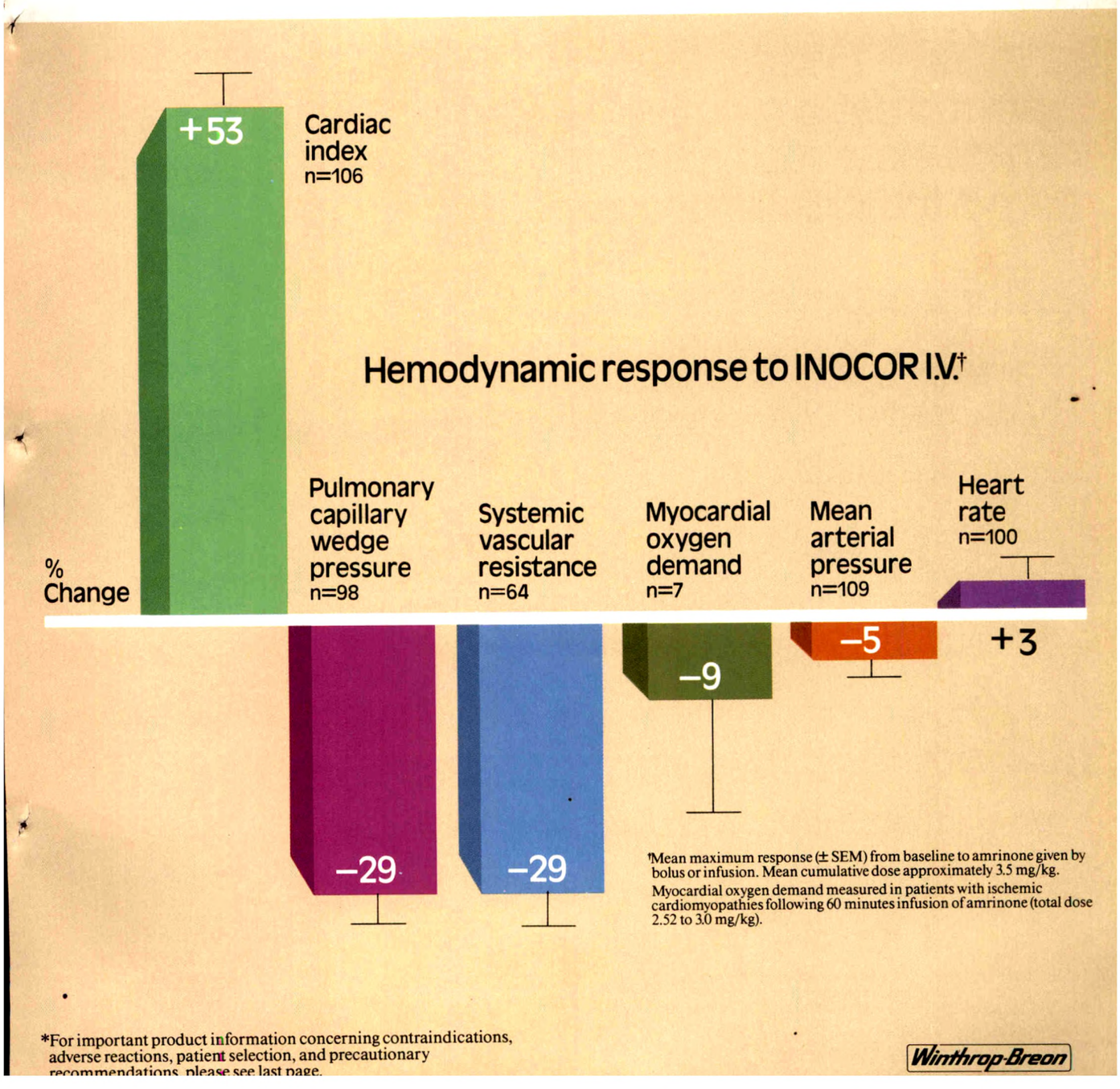

†Mean maximum response (± SEM) from baseline to amrinone given by bolus or infusion. Mean cumulative dose approximately 3.5 mg/kg.
Myocardial oxygen demand measured in patients with ischemic cardiomyopathies following 60 minutes infusion of amrinone (total dose 2.52 to 3.0 mg/kg).

*For important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations, please see last page.

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Symptomatic relief with INOCOR I.V. can be expected following hemodynamic improvement

Patient progress is reflected by:

- Increase in cardiac output
- Reduction in pulmonary capillary wedge pressure
- Improvement in clinical symptomatology
  - Dyspnea
  - Orthopnea
  - Paroxysmal nocturnal dyspnea
  - Fatigue

Benefits sustained during therapy

- No evidence of tachyphylaxis

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INOCOR I.V. adverse reaction profile

In clinical studies with intravenous INOCOR in 462 patients, the following adverse reaction profile emerged:

Adverse reaction		Incidence (%)
Arrhythmia		3.0
Thrombocytopenia		2.4
Gastrointestinal	Nausea	1.7
	Vomiting	0.9
	Abdominal pain	0.4
	Anorexia	0.4
Hypotension		1.3
Fever		0.9
Liver enzyme alterations		0.2
Chest pain		0.2
Burning at the site of injection		0.2

- Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.
- In closely monitored clinical trials, patients with amrinone-related thrombocytopenia whose platelet counts were not allowed to remain depressed, showed no bleeding phenomena.
- Hepatotoxicity (liver enzyme alterations) has been observed following long term oral therapy. It has been observed, in a limited experience (0.2%), following intravenous administration of amrinone.
- While hypersensitivity has not been attributed to amrinone, this possibility should be considered with repeated administration.
- Until additional experience is available, concurrent administration with disopyramide should be undertaken with caution.

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How to use INOCOR

1. Initiate therapy with a 0.75 mg/kg bolus given slowly over 2 to 3 minutes.
2. Continue therapy with maintenance infusion between 5 and 10 μg/kg/min.
3. Based on clinical response, an additional bolus injection of 0.75 mg/kg may be given 30 minutes after the initiation of therapy.
4. The rate of infusion usually ranges from 5 to 10 μg/kg/min such that the recommended total daily dose (including boluses) does not exceed 10 mg/kg. A limited number of patients studied at higher doses support a dosage regimen up to 18 mg/kg/day for shortened durations of therapy.
5. The rate of administration and the duration of therapy should be adjusted according to the patient's response. The physician may wish to reduce or titrate the infusion downward based on clinical responsiveness or untoward effects.

- INOCOR may be administered as supplied or diluted in normal or half-normal saline to a concentration of 1 mg/mL to 3 mg/mL.
- INOCOR should not be diluted with solutions that contain dextrose (glucose).
- A chemical interaction occurs slowly over a 24-hour period when the intravenous solution of INOCOR is mixed directly with dextrose (glucose)-containing solutions.
- INOCOR may be injected into running dextrose (glucose) lines.
- All diluted solutions should be used within 24 hours.

For important product information concerning contraindications, adverse reactions, patient selection, and precautionary

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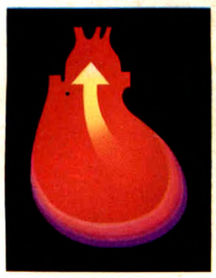

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- Hemodynamics rapidly improved
- Appropriate for hypertensive, normotensive, or hypotensive patients who have adequate filling pressure and those with myocardial ischemia
- Adverse reactions manageable and reversible
- Duration of therapy depends on patient responsiveness
- Dependable, controlled response with intravenous infusion
- Easy to administer

For important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations, please see next page.

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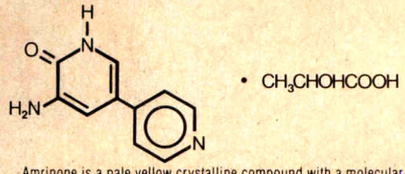
INOCOR® LACTATE INJECTION

Brand of amrinone lactate
Sterile Intravenous Solution

DESCRIPTION: INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents distinct from digitalis glycosides or catecholamines. Amrinone lactate is designated chemically as 5-Amino [3,4′-bipyridin]-6(1*H*)-one lactate and has the following structure:



Amrinone is a pale yellow crystalline compound with a molecular weight of 187.2 and an empirical formula of $C_{10}H_9N_3O$. Each mole of lactic acid has a molecular weight of 90.08 and an empirical formula of $C_3H_6O_3$. The solubilities of amrinone at pH's 4.1, 6.0, and 8.0 are 25, 0.9, and 0.7 mg/mL, respectively.

INOCOR lactate injection is available as a sterile solution in 20 mL ampuls for intravenous administration. Each mL contains INOCOR lactate equivalent to 5 mg of base and 0.25 mg of sodium metabisulfite added as a preservative in Water for Injection. All dosages expressed in the package insert are expressed in terms of the base, amrinone. The pH is adjusted to between 3.2 to 4.0 with lactic acid or sodium hydroxide. The total concentration of lactic acid can vary between 5.0 mg/mL and 7.5 mg/mL.

CLINICAL PHARMACOLOGY: INOCOR lactate injection is a positive inotropic agent with vasodilator activity, different in structure and mode of action from either digitalis glycosides or catecholamines.

The mechanism of its inotropic and vasodilator effects has not been fully elucidated.

With respect to its inotropic effect, experimental evidence indicates that it is not a beta-adrenergic agonist. It inhibits myocardial cyclic adenosine monophosphate phosphodiesterase (c-AMP) activity and increases cellular levels of c-AMP. Unlike digitalis, it does not inhibit sodium-potassium adenosine triphosphatase activity.

With respect to its vasodilatory activity, INOCOR reduces afterload and preload by its direct relaxant effect on vascular smooth muscle.

Pharmacokinetics: Following intravenous bolus (1 to 2 minutes) injection of 0.68 mg/kg to 1.2 mg/kg to normal volunteers, INOCOR had a volume of distribution of 1.2 liters/kg; and following a distributive phase half-life of about 4.6 minutes in plasma, had a mean apparent first-order terminal elimination half-life of about 3.6 hours. In patients with congestive heart failure receiving infusions of INOCOR the mean apparent first-order terminal elimination half-life was about 5.8 hours.

Amrinone has been shown in one study to be 10% to 22% bound to human plasma protein by ultrafiltration in vitro, and in another study 35% to 49% bound by either ultrafiltration or equilibrium dialysis.

The primary route of excretion in man is *via* the urine as both amrinone and several metabolites (N-glycolyl, N-acetate, O-glucuronide and N-glucuronide). In normal volunteers, approximately 63% of an oral dose of ^{14}C-labelled amrinone was excreted in the urine over a 96-hour period. In the first 8 hours, 51% of the radioactivity in the urine was amrinone with 5% as the N-acetate, 8% as the N-glycolate, and less than 5% for each glucuronide. Approximately 18% of the administered dose was excreted in the feces in 72 hours.

In a 24-hour nonradioactive intravenous study, 10% to 40% of the dose was excreted in urine as unchanged amrinone with the N-acetyl metabolite representing less than 2% of the dose.

In congestive heart failure patients, after a loading bolus dose, steady-state plasma levels of about 2.4 μg/mL were able to be maintained by an infusion of 5 μg/kg/min to 10 μg/kg/min. In some congestive heart failure patients, with associated compromised renal and hepatic perfusion, it is possible that plasma levels of amrinone may rise during the infusion period; therefore, in these patients, it may be necessary to monitor the hemodynamic response and/or drug level. The principal measures of patient response include cardiac index, pulmonary capillary wedge pressure, central venous pressure, and their relationship to plasma concentrations. Additionally, measurements of blood pressure, urine output, and body weight may prove useful, as may such clinical symptoms as orthopnea, dyspnea, and fatigue.

Pharmacodynamics: In patients with depressed myocardial function, INOCOR lactate injection produces a prompt increase in cardiac output due to its inotropic and vasodilator actions.

Following a single intravenous bolus dose of INOCOR of 0.75 mg/kg to 3 mg/kg in patients with congestive heart failure, dose-related maximum increases in cardiac output occur (of about 28% at 0.75 mg/kg to about 61% at 3 mg/kg). The peak effect occurs within 10 minutes at all doses. The duration of effect depends upon dose, lasting about 1/2 hour at 0.75 mg/kg and approximately 2 hours at 3 mg/kg.

Over the same range of doses, pulmonary capillary wedge pressure and total peripheral resistance show dose-related decreases (mean maximum decreases of 29% in pulmonary capillary wedge pressure and 33% in systemic vascular resistance). At doses up to 3.0 mg/kg dose-related decreases in diastolic pressure (up to 13%) have been observed. Mean arterial pressure decreases (9.7%) at a dose of 3.0 mg/kg. The heart rate is generally unchanged.

The changes in hemodynamic parameters are maintained during continuous intravenous infusion and for several hours thereafter.

INOCOR lactate injection is effective in fully digitalized patients without causing signs of cardiac glycoside toxicity. Its inotropic effects are additive to those of digitalis. In cases of atrial flutter/fibrillation, it is possible that INOCOR may increase ventricular response rate because of its slight enhancement of A/V conduction. In these cases, prior treatment with digitalis is recommended.

Improvement in left ventricular function and relief of congestive heart failure in patients with ischemic heart disease have been observed. The improvement has occurred without inducing symptoms or electrocardiographic signs of myocardial ischemia.

At constant heart rate and blood pressure, increases in cardiac output occur without measurable increases in myocardial oxygen consumption or changes in arterio-venous oxygen difference.

Inotropic activity is maintained following repeated intravenous doses of INOCOR. INOCOR administration produces hemodynamic and symptomatic benefits to patients not satisfactorily controlled by conventional therapy with diuretics and cardiac glycosides.

INDICATIONS AND USAGE: INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS: INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS: General: INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

USE IN ACUTE MYOCARDIAL INFARCTION: No clinical trials have been carried out in patients in the acute phase of postmyocardial infarction. Therefore, INOCOR lactate injection is not recommended in these cases.

Laboratory Tests: Fluid and Electrolytes: Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

Drug Interactions: In a relatively limited experience, no untoward clinical manifestations have been observed in patients in which INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides; lidocaine, quinidine; metoprolol, propranolol; hydralazine, prazosin; isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril; heparin, warfarin; potassium supplements; insulin; diazepam.

One case report of excessive hypotension has been reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with NORPACE® (disopyramide) should be undertaken with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The 1-year interim evaluation of the 2-year oral carcinogenicity study on F344 rats indicated no tumor induction at that time.

The mouse micronucleus test (at 7.5 to 10 times the maximum human dose) and the Chinese hamster ovary chromosome aberration assay were positive indicating both clastogenic potential and suppression of the number of polychromatic erythrocytes. However, the Ames Salmonella assay, mouse lymphoma study, and cultured human lymphocyte metaphase analysis were all negative. The clastogenic effects are in contrast to negative results obtained in the rat male and female fertility studies, and a three-generation study in rats, both with oral dosing.

Slight prolongation of the rat gestation period was seen in these studies at dose levels of 50 mg/kg/day and 100 mg/kg/day. Dystocia occurred in dams receiving 100 mg/kg/day resulting in increased numbers of stillbirths, decreased litter size, and poor pup survival.

Pregnancy Category C: In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg which were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily intravenous dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Thrombocytopenia: Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm³ or normal limits in 2.4 percent of the patients.

It is more common in patients receiving prolonged therapy. To date, in closely-monitored clinical trials, in patients whose platelet counts were not allowed to remain depressed, no bleeding phenomena have been observed.

Platelet reduction is dose dependent and appears due to a decrease in platelet survival time. Several patients who developed thrombocytopenia while receiving amrinone had bone marrow examinations which were normal. There is no evidence relating platelet reduction to immune response or to a platelet activating factor.

Gastrointestinal Effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular Effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic Toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following intravenous administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis and ascites (1 case), myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (1 case) and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (1 case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged so that attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

Management of Adverse Reactions: Platelet Count Reductions: Asymptomatic platelet count reduction (to <150,000/mm³) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than pre-drug levels without any clinical sequelae. Pre-drug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm³ occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pre-treatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal Side Effects: While gastrointestinal side effects were seen infrequently with intravenous therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic Toxicity: In clinical experience to date with intravenous administration, hepatotoxicity has been observed rarely. If acute marked alterations in liver enzymes occur together with clinical symptoms suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone, reduce dosage, or discontinue the drug based on the usual benefit/risk considerations.

OVERDOSAGE: Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

In rats, the LD_{50} of amrinone, as the lactate salt, was 102 mg/kg or 130 mg/kg intravenously in two different studies and 132 mg/kg orally (intragastrically); as a suspension in aqueous gum tragacanth the oral LD_{50} was 239 mg/kg.

DOSAGE AND ADMINISTRATION: INOCOR lactate injection may be administered as supplied or diluted in normal, or half normal saline solution to a concentration of 1 mg/mL to 3 mg/mL. Diluted solutions should be used within 24 hours.

INOCOR lactate injection may be injected into running dextrose (glucose) infusions through a Y-Connector or directly into the tubing where preferable.

A chemical interaction occurs slowly over a 24-hour period when the intravenous solution of INOCOR lactate injection is mixed directly with dextrose (glucose)-containing solutions. **THEREFORE, INOCOR LACTATE INJECTION SHOULD NOT BE DILUTED WITH SOLUTIONS THAT CONTAIN DEXTROSE (GLUCOSE) PRIOR TO INJECTION.**

The following procedure is recommended for the administration of INOCOR lactate injection:

1. Initiate therapy with a 0.75 mg/kg bolus given slowly over 2 to 3 minutes.
2. Continue therapy with a maintenance infusion between 5 μg/kg/min and 10 μg/kg/min.
3. Based on clinical response, an additional bolus injection of 0.75 mg/kg may be given 30 minutes after the initiation of therapy.
4. The rate of infusion usually ranges from 5 μg/kg/min to 10 μg/kg/min such that the recommended total daily dose (including boluses) does not exceed 10 mg/kg. A limited number of patients studied at higher doses support a dosage regimen up to 18 mg/kg/day for shortened durations of therapy.
5. The rate of administration and the duration of therapy should be adjusted according to the response of the patient. The physician may wish to reduce or titrate the infusion downward based on clinical responsiveness or untoward effects.

The above dosing regimens can be expected to place most patient's plasma concentration of amrinone at approximately 3 μg/mL. Increases in cardiac index show a linear relationship to plasma concentration of a range of 0.5 μg/mL to 7 μg/mL. No observations have been made at greater plasma concentrations.

Patient improvement may be reflected by increases in cardiac output, reduction in pulmonary capillary wedge pressure, and such clinical responses as a lessening of dyspnea and an improvement in other symptoms of heart failure, such as orthopnea and fatigue.

Monitoring central venous pressure (CVP) may be valuable in the assessment of hypotension and fluid balance management. Prior correction or adjustment of fluid/electrolytes is essential to obtain satisfactory response with amrinone.

Parenteral drug products should be inspected visually and should not be used if particulate matter or discoloration is observed.

HOW SUPPLIED: Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equivalent to 5 mg base and 0.25 mg sodium metabisulfite in Water for Injection. The pH of INOCOR lactate injection is adjusted to a range of 3.2 to 4.0 with lactic acid or sodium hydroxide.

Protect INOCOR lactate ampuls from light. Ampul packaging is light resistant for protection during storage.

Store at room temperature.

NOTE: Parenteral drug products should be inspected visually and should not be used if particulate matter or discoloration is observed.

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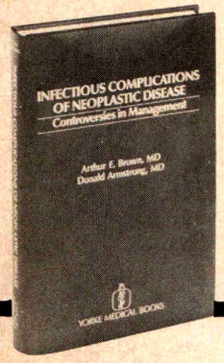

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Value of Arm Exercise Testing in Detecting Coronary Artery Disease

GARY J. BALADY, MD, DONALD A. WEINER, MD, CAROLYN H. McCABE, BS, and THOMAS J. RYAN, MD

Alternative methods of exercise testing are needed for patients with vascular, orthopedic or neurologic conditions who cannot perform leg exercise. To determine the sensitivity of arm exercise in detecting coronary artery disease (CAD), 30 patients with angina pectoris performed both arm ergometry and treadmill testing before coronary angiography. All patients had at least 70% diameter reduction in 1 or more major coronary arteries. Ischemic ST depression ($\geq$1 mm) or angina occurred more frequently (86%, 26 patients) with leg exercise than with arm exercise (40%, 12 patients). There was no significant difference in peak rate-pressure product achieved with either test, although the peak oxygen consumption was greater during leg exercise than during arm exercise (18 vs 13 ml/kg/min, respectively, p <0.001). For concordantly positive tests, the oxygen consumption at onset of ischemia was significantly lower during arm testing than during leg testing (12 vs 17 ml/kg/min, respectively, p <0.001). There was no significant difference in heart rate during either test at onset ischemia. Thus, arm exercise testing is a reasonable, but not equivalent, alternative to leg exercise testing in patients who cannot perform leg exercise.

(Am J Cardiol 1985;55:37–39)

Exercise testing is a standard noninvasive method used in the evaluation and management of patients with suspected coronary heart disease (CAD).[1] Many conditions, such as neurologic, vascular or orthopedic impairment of the lower extremities, often preclude performing an adequate treadmill or bicycle test. Dynamic arm exercise testing may be a valuable alternative to leg exercise in such patients,[2–4] although the sensitivity of this method of stress testing in detecting CAD is unknown. The present study evaluates the sensitivity of arm exercise testing in patients with angiographically proved CAD and compares the physiologic responses of dynamic arm and leg exercise in 30 patients.

Methods

Study population: The study group consisted of 30 patients referred for diagnostic evaluation of suspected or known CAD who could undergo arm and leg exercise testing and coronary angiography. Clinical data recorded included age, sex, type and severity of chest pain according to the Canadian Cardiovascular Society classification[5] and history of myocardial infarction and medications used.

Testing: All patients underwent 2 maximal, symptom-limited, graded exercise tests using an arm ergometer and treadmill, performed in random fashion alternating between morning and afternoon periods to avoid diurnal variation in exercise tolerance, so that 14 (46%) of the patients performed arm ergometry initially. Treadmill testing was performed using a Marquette Series 1800 treadmill electronically programmed according to the Bruce protocol.[6] The patients performed arm ergometry using a Quinton imaging table with an electronically braked bicycle ergometer, which was modified for arm exercise with replacement of the pedals with rubber handles. The patients were seated upright, with feet flat on the ground and the fulcrum of the handle was adjusted to shoulder height. They performed arm exercise initially at a workload of 35 W and continued at incremental workloads of 25 W every 3 minutes until the test was terminated.

A 12-lead electrocardiogram and blood pressure were recorded for both tests at rest, at 3-minute intervals during exercise, at peak exercise, and during recovery for at least 10 minutes. The blood pressure during arm exercise was measured with the patient dropping 1 arm to allow measurement, while arm cranking was continued with the other arm. Blood pressure recordings usually took no more than 20 seconds. The endpoints of both exercise tests were the development of either moderately severe angina pectoris, dyspnea, fatigue, complex ventricular arrhythmias or more than 3 mm of ST-segment depression on the monitoring electrocardiogram. An ischemic ST-segment response was defined as either 1 mm or

From the Evans Memorial Department of Clinical Research and The Department of Medicine, University Hospital, Boston University Medical Center, Boston, Massachusetts. Manuscript received June 18, 1984; revised manuscript received August 16, 1984, accepted August 20, 1984.

Address for reprints: Donald A. Weiner, MD, Section of Cardiology, University Hospital, 75 East Newton Street, Boston, Massachusetts 02118.

TABLE I Characteristics of Exercise Test Response

	Arm (n = 30)	Leg (n = 30)
Heart rate (beats/min)		
Rest	60 ± 11	63 ± 13
Peak	101 ± 18*	109 ± 17
Systolic blood pressure (mm Hg)		
Rest	128 ± 17	125 ± 18
Peak	161 ± 20	152 ± 22
Peak rate-pressure product (bpm × mm Hg × 10^3)	16 ± 4	16 ± 4
Peak VO_2 (ml/kg/min)	13 ± 5†	18 ± 1

* $p < 0.01$; † $p < 0.001$.
VO_2 = oxygen consumption.

more of horizontal or downsloping ST-segment depression or 1.5 mm of upsloping ST-segment depression from the isoelectric baseline that lasted at least 80 ms after the J point, for 3 consecutive beats during exercise or recovery. Exercise variables analyzed included the presence, magnitude and configurations of ST-segment depression; heart rate and oxygen consumption at onset of angina and ST depression; changes in heart rate and systolic blood pressure from rest to peak exercise; maximal heart rate and systolic blood pressure achieved, and their product; and peak oxygen consumption.

A Beckman metabolic cart comprising a volume transducer, a Beckman OM-11 oxygen analyzer, and a Beckman VO_2 carbon dioxide analyzer was used to determine minute oxygen consumption and minute carbon dioxide production. Oxygen and carbon dioxide concentrations in expired air were delivered through a mouthpiece, equipped with a low-resistance 3-way valve to a mixing chamber, volume transducer and gas analyzer.

Selective coronary arteriography used the brachial[7] or percutaneous femoral techniques,[8] and cineangiograms were recorded in multiple projections. Significant CAD was defined as at least 70% diameter narrowing of 1 or more major coronary arteries.

Statistical analysis: Comparisons of patient data were performed using chi-square analysis or the paired *t* test. Differences with probability values ($p < 0.05$) were considered to be statistically significant. Statistical methods were those outlined by Colton.[9]

Results

Population: The patient population consisted of 29 men and 1 woman, mean age 59 ± 9 years (range 40 to 71). All patients gave a history of exertional angina and 11 had class III or IV symptoms. A documented previous myocardial infarction was found in 12 patients (40%). Medications taken at the time of testing included β-adrenergic receptor blocking agents in 27 patients (90%) and calcium channel antagonists in 19 (64%). No patient was taking digitalis and no patient had either left ventricular hypertrophy or left bundle branch block on the electrocardiogram at rest. At cardiac catheterization, all patients had significant CAD: 8 (27%) had 1-vessel CAD, 9 (30%) had 2-vessel CAD, 11 (35%) had 3-vessel CAD, and 2 (8%) had left main CAD.

Exercise responses: Responses to both arm and leg exercise tests are listed in Tables I and II. Endpoints of exercise were moderate angina (20% during arm, 47% during leg) and fatigue (80% during arm, 53% during leg). The same endpoint for exercise during arm and leg testing was reached in 73% (22 of 30) of paired tests performed. Ischemic responses—angina or ST-segment depression (Fig. 1)—were demonstrated in 26 patients (86%) during leg exercise, and in 12 patients (40%) during arm exercise, despite a similar peak rate-pressure product during both tests. There was, however, a small difference in the peak heart rate attained during leg testing compared with arm testing (109 ± 17 vs 101 ± 8 beats/min, respectively, $p < 0.01$). Peak oxygen consumption during arm exercise was significantly less than that during leg exercise (13 vs 18 ml/kg/min, respectively, $p < 0.001$). Twelve patients (47%) had ischemic responses during both arm and leg exercise tests. There was no significant difference between the heart rate at the onset of angina (89 beats/min for arm exercise and 97 beats/min for leg exercise) or at the onset of ST-segment depression (99 beats/min for arm exercise vs 102 beats/min for leg exercise). However, measured oxygen consumption was higher for leg exercise than for arm exercise both at the onset of angina and at the onset of ST-segment depression (Fig. 2).

TABLE II Positive Tests Stratified By Extent of Coronary Artery Disease

No. of Diseased Vessels	No. of Pts.	Arm Test	Leg Test
1	8	3 (38%)	5 (62%)
2	9	5 (56%)	9 (100%)
3	11	3 (27%)	7 (64%)
Left main	2	1 (50%)	1 (50%)

Discussion

The results of this study demonstrate that important differences exist between dynamic arm and leg exercise, which are reflected in the exercise test response. Arm exercise testing was less sensitive than leg exercise testing in detecting CAD. Despite differences in the ischemic response, peak rate-pressure product for arm and leg exercise were not significantly different, although peak oxygen consumption for arm exercise was less than that for leg exercise.

Other investigators have examined the ischemic response to arm exercise in varying detail, and have had

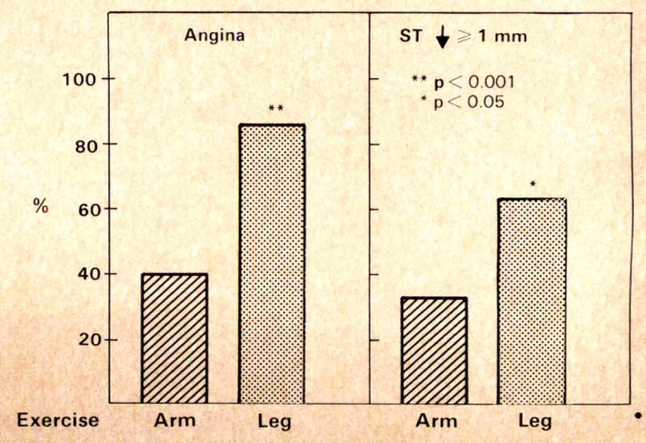

FIGURE 1. Ischemic responses to exercise.

conflicting results. Clausen and Trap-Jensen[10] studied 29 patients with angina who did not undergo cardiac catheterization. They found concordantly positive tests for angina in 11 of 12 patients who did both arm and leg exercise, although the rate-pressure product threshold for angina during arm exercise was greater than that of leg exercise. However, the ST-segment response during exercise was not examined. DeBusk et al,[11] in a study of 40 men who had previous myocardial infarctions, examined the ischemic response to arm and leg ergometry. The sensitivity of detecting CAD in this population was low for both tests (18% for arm vs 25% for leg, difference not significant). There was no difference in the peak rate-pressure product for each test. The sensitivities reported herein were probably remarkably low for both tests, because all subjects being tested had had a previous myocardial infarction and may not have had active ischemia. Schwade et al[3] also noted no difference in the sensitivity of arm compared with leg exercise in detecting CAD in a population of 33 men, although the extent of CAD and presence of angina were not defined in that population. In a study of 21 patients, Shaw et al[2] also found no difference in the ischemic response to arm ergometry vs treadmill testing. However, since all patients did not undergo cardiac catheterization to determine the extent of CAD, the actual sensitivities of either test could not be determined.

The physiologic responses to arm and leg dynamic exercise have been reported previously in several studies.[2–4,10–12] All studies have noted that the peak workload for arm exercise is significantly less than that of leg exercise. This is not surprising, considering the smaller muscle mass of upper extremities compared with lower extremities. The heart rate, systolic blood pressure, and rate-pressure product were higher for a given workload during arm exercise compared with leg exercise. This may be due to an increased sympathetic tone during arm exercise compared with leg exercise. Also, there is less vasodilation during arm work because of the relatively small mass of exercising muscle, and this could account for a higher peripheral resistance and, therefore, a greater blood pressure during arm exercise at any given amount of work. Our data suggest that changes in rate-pressure product at peak exercise did not reflect total myocardial oxygen consumption, since we found no significant difference in the rate-pressure product during peak arm and leg exercise despite a significant difference in ischemic response. Other determinants of myocardial oxygen consumption include myocardial contractility and the level of myocardial wall tension.[13] Wall tension could be substantially greater during leg exercise due to augmented venous return from the larger contracting muscles, leading to an increased left ventricular end-diastolic volume, as compared with upper-extremity exercise. Alternatively, vasodilatation of a greater number of resistance vessels during leg exercise, which leads to an overall decrease in peripheral resistance, may result in a net lowering of wall tension. Contractility may also be greater during leg exercise due to increases in left ventricular end-diastolic volume, or due to increased sympathetic stimulation of the myocardium. The use of radionuclide ventriculography or echocardiography may help to resolve these differences.

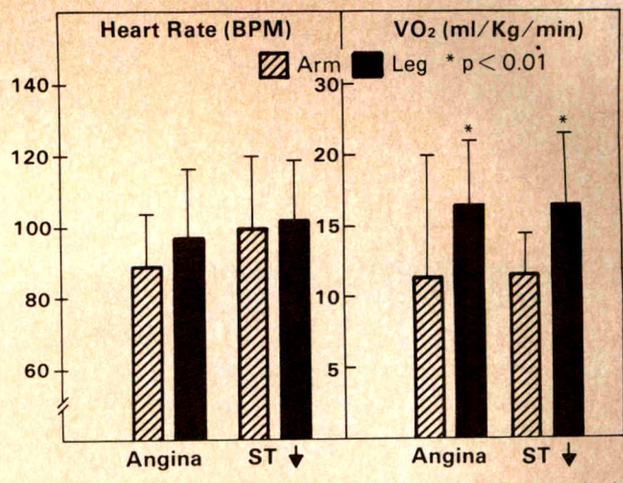

FIGURE 2. Exercise variables at the onset of ischemia for concordantly positive tests. VO_2 = oxygen consumption.

Some limitations of our study protocol should be considered. The patients continued to take their antianginal medications throughout the test period. Although the use of paired testing should negate medication effect, the medications could alter the physiologic responses to arm and leg exercise differently. Second, the patients were more familiar and facile with upright walking exercise than with arm cranking exercise, and this may also account for some degree of difference in the observed sensitivities. However, all patients did achieve similar peak rate-pressure products in both tests. Finally, the peak systolic blood pressure might be more subject to error during arm exercise testing because of technical problems.

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Coronary Risk Factors and Their Pathway of Action Through Coronary Raised Lesions, Coronary Stenoses and Coronary Death

Multivariate Statistical Analysis of an Autopsy Series: The Oslo Study

INGAR HOLME, PhD, LARS A. SOLBERG, MD, LISA WEISSFELD, PhD, ANDERS HELGELAND, MD, INGVAR HJERMANN, MD, PAUL LEREN, MD, JACK P. STRONG, MD, and O. DALE WILLIAMS, PhD

From 1972 to 1973, 16,202 Oslo men, aged 40 to 49 years, were examined for cardiovascular disease and coronary heart disease (CHD) risk factors. This report describes the results of autopsy examinations from 204 of 471 men who died in this cohort with regard to associations between selected risk factors and (1) raised coronary atherosclerotic lesions (RL), (2) coronary artery stenosis, and (3) CHD death. Total serum cholesterol and blood pressure levels were positively associated with all 3 measures of coronary atherosclerosis and its complications, both in univariate and multivariate analyses, whereas high-density lipoprotein (HDL) cholesterol was highly and inversely related. Triglyceride levels, cigarette smoking, social class and physical activity at work and at leisure were not significantly associated with either of the 3 measures. When RL was added to the model with stenosis as the dependent variable, the risk factors no longer appeared as independent; this is consistent with the hypothesis that these factors, when significant, work through the development of RL to produce stenosis. HDL cholesterol was the only risk factor independently and significantly associated with CHD death when RL or stenosis or both were put into the model for CHD. This points to the possibility of HDL cholesterol also working through mechanisms other than the prevention of RL and stenosis toward CHD death.

(Am J Cardiol 1985;55:40–47)

The associations between coronary risk factors and clinically manifest coronary heart disease (CHD) have been established in numerous studies. The pathway of action has been hypothesized as being through the building of coronary atherosclerotic raised lesions (RL) and stenosis, finally resulting in occlusion, ischemia and myocardial infarction, angina pectoris or sudden death due to CHD. Many coronary risk factors are also known to be associated with RL. However, for some factors, such as cigarette smoking and physical activity at leisure, the associations are weaker or less consistent than those found in most clinical data.[1–5] Total serum cholesterol and blood pressure have consistently been associated with CHD in autopsy and clinical studies.[1–5] One study has also shown that high-density lipoprotein cholesterol (HDL-C) is inversely and strongly related to coronary RL.[2]

The number of coronary arteries with stenosis is a factor predictive of subsequent CHD, evaluated either angiographically or by autopsy.[6–9] Thus, risk factors for stenosis are also of interest. Associations between risk factors and RL similar to those between risk factors and

From the Life Insurance Companies' Institute for Medical Statistics, Department of Pathology and Outpatient Clinic at Ullevaal Hospital, Oslo, Norway; Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and Department of Pathology, Louisiana State University Medical Center, New Orleans, Louisiana.
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Address for reprints: Ingar Holme, PhD, Life Insurance Companies' Institute for Medical Statistics, P.O. Box 6, Ullevaal Hospital, 0407 Oslo 4, Norway.

stenosis are presented herein. This study is an assessment of the importance of risk factors with respect to stenosis in addition to that of coronary RL, the hypothesis being that the impact of risk factors on stenoses is mediated through RL.

Methods

The Oslo Study has been described elsewhere.[10] In short, all Oslo men aged 40 to 49 years in 1972 were invited to a screening examination for assessment of cardiovascular risk (65% attendance proportion). The examination included blood pressure measurements and blood samples (nonfasting) for lipid analyses. Information on known cardiovascular disease or diabetes, physical activity both at work and at leisure and current and previous smoking habits was collected. HDL-C was derived from frozen specimens later in the study for 88% of the available autopsy series.[11]

The grading of atherosclerosis in the coronary arteries has been described elsewhere.[12] Briefly, coronary arteries were opened longitudinally and stenosis was defined as present whenever a reduction of the luminal diameter in an artery was more than 40% (judged visually). This evaluation was done for each of the 3 major coronary arterial branches. Coronary atherosclerotic raised lesions (i.e., the sum of fibrous plaques, complicated and calcified lesions), were graded by a specially trained team of pathologists at the Department of Pathology, Louisiana State University, New Orleans, who had no clinical or risk factor information about the cases.

A CHD death was recorded whenever 1 of 3 events happened: sudden death with or without thrombotic coronary occlusion but with severe stenosed coronary atherosclerosis, recent morphologic myocardial infarction, and myocardial scars after previous myocardial infarction.

This autopsy series is a selection of 204 consecutive cases gathered from the start of the study until January 1, 1981, at the Department of Pathology, Ullevaal Hospital, out of the total cohort of 16,202 men who attended the screening.

Statistical methods: In Table I the dependent variables of the study are defined. A raised lesion is measured by a percentage, whereas CHD is defined as being present or absent. Stenosis as a dependent variable is treated in several ways. In 1 analysis, the variable "Sten" is analyzed by an ordinal logistic regression model with possibly different intercepts, but common regression coefficients in each group of stenosis for all independent variables. In another, each of the variables, Sten 1, 2 and 3 was analyzed separately in relation to the independent variables to examine lack of homogeneity in the regression coefficients for increasing severity of stenosis. However, here some parts (Table I) of the data set had to be deleted to use the dichotomous logistic regression model. The independent variables were total serum cholesterol (CHOL), HDL-C, cholesterol ratio [HDL-C/(CHOL-HDL-C)], serum triglycerides, systolic and diastolic blood pressure, number of daily cigarettes, degree of physical activity at work and at leisure and social class.[13]

The strategy of analysis has been first to look for "outliers" and skewed distributions in all variables. All factors appeared to be fairly symmetric except triglycerides, which, after transformation to natural logarithm, ln(Trig), was approximately normal. The percentage of raised lesions was flat over the entire range, so some computations were done with the arcsine raised lesions transformation, but none of the conclusions changed. Results are therefore presented with untransformed raised lesions but with ln transformed triglycerides. No "outliers" were detected.

Systolic and diastolic blood pressure are highly correlated in this series and are entered only one at a time as independent variables in the multivariate analyses. HDL-C and the cholesterol ratio never entered simultaneously. This multicolinearity problem also appears with respect to total cholesterol and the cholesterol ratio. In the tables, only data for systolic blood pressure, total cholesterol and HDL-C are presented. Possible differences with regard to diastolic blood pressure or cholesterol ratio are mentioned.

TABLE I Definition of Dependent Variables in the Study

Variable	Definition
CHD	1 if CHD death; 0 otherwise
RL	Total percent involvement of the 3 main coronary arteries with raised lesions based on a separate classification for each of the 3 main arterial branches
Sten	Number of arteries involved with at least 1 stenosis (0, 1, 2, 3)
Sten 1	1 if any of the 3 coronary arteries is involved with at least 1 stenosis; 0 otherwise
Sten 2	1 if at least 2 of the coronary arteries are involved with at least 1 stenosis; 0 otherwise, excluding all men with 1 artery only involved with stenosis
Sten 3	1 if all 3 coronary arteries are involved with at least 1 stenosis; 0 otherwise, excluding all men with 1 or 2 arteries involved with stenosis

CHD = coronary heart disease; RL = raised lesions.

Raised lesions were analyzed by multiple linear regression model by fitting 10 arbitrarily chosen, separate sets of independent variables to RL. In the analysis of the 3 stenosis variables—Sten 1, Sten 2, Sten 3—the multiple logistic regression model was applied. For each of the 10 sets of variables (same as for raised lesions), the variable raised lesions were entered or deleted as an explanatory variable for stenoses. This addresses the question of whether it is likely that risk factors work through raised lesions in developing stenosis or if they have their own specific pathway of action different from building raised lesions. Ordinal logistic regression was performed with Sten as a dependent variable, allowing for different intercepts but with the same regression coefficient for each risk factor across the 4 stenosis groups.[14] In this way, all the data could be used.

In the final analysis of CHD, again the multiple logistic regression model was applied with the same set of risk factor models, with or without raised lesions or stenosis, using Sten as the conditioning variable. In a few analyses both raised lesions and stenoses were added to the risk factor set.

In this report, analyses have been presented for only the subset of the total cohort for which full information of all 10 risk factors was available. However, for models that involved HDL-C, analyses could be performed only on a subset of men. A few analyses were made in the so-called basal group, which consists of those who died from other than cardiovascular disease, with raised lesions and stenosis as dependent variables. Again, associations appeared to be more pronounced for factors that were already significant, but no new factor entered which could alter the main conclusions.

In the analysis with CHD death as the endpoint, some searches for interaction terms between raised lesions or stenosis and some risk factors were performed, but such multiplicative terms did not appear to be significant in any of the analyses.

Interaction terms between lipids and blood pressure were tested with raised lesions and stenosis as dependent variables. Some of the factors, such as CHD death, stenosis and social class, are discrete so that t tests for significant 0-order corre-

TABLE II Mean Values (± Standard Deviation) for Some Coronary Risk Factors in Autopsied and Nonautopsied Cases of Death from Start of Study Until December 31, 1980 (Autopsy Proportion: 35%)

Risk Factor*	Autopsy (n = 204)	Non-Autopsy (n = 378)	Total
Serum cholesterol (mg/dl)	288.6 ± 46.6	282.3 ± 58.6	284.5 ± 54.8
Triglycerides (mmol/l)	2.58 ± 1.46	2.51 ± 1.55	2.54 ± 1.52
Systolic BP (mm Hg)	144.4 ± 20.4	142.6 ± 21.8	143.2 ± 21.4
Diastolic BP (mm Hg)	92.1 ± 12.7	91.3 ± 14.0	91.6 ± 13.6
No. of cigarettes/day	10.5 ± 8.7	9.4 ± 9.6	9.8 ± 9.3
Coronary risk score†	21.6 ± 27.9	19.9 ± 29.5	20.5 ± 28.9

* High-density lipoprotein cholesterol not available for nonautopsied cases.
† Based on cholesterol, systolic blood pressure and cigarette smoking.
BP = blood pressure.

lations cannot be interpreted as easily as in the continuous, normal case.

Results

Table II lists mean values of some selected risk factors in autopsied and nonautopsied cases among those who attended screening. There was a slight, nonsignificant excess risk present in the autopsied cases ($p > 0.10$).

Table III lists 0-order correlation coefficients between all dependent and independent variables together with mean values and standard deviations. The indicated high intercorrelation between the 3 dependent variables was expected and has been analyzed in more detail elsewhere.[9] None of the independent variables appear to be especially intercorrelated except diastolic and systolic blood pressure, HDL-C and the cholesterol ratio, and cholesterol and the cholesterol ratio.

Ten models were selected as being potentially interesting with regard to how groups of risk factors act on the various dependent variables. For each model, the variable raised lesions is added or deleted in the analyses with stenosis as the dependent variable. The same is repeated when CHD is the dependent variable, alternating also with stenosis as an independent variable.

In Table IV these 10 models for raised lesions are presented in terms of partial linear regression coefficients, their t values, and the R^2 values. Also in this extended data set, cigarette smoking could not be shown to be associated with coronary raised lesions, either marginally (Table III) or adjusted for social class or for serum cholesterol. Serum cholesterol level was highly significantly associated with raised lesions, as were HDL-C and systolic blood pressure. Systolic blood pressure associated significantly over and above that of cholesterol and HDL-C and the same was true for HDL-C, keeping the other 2 in the model. Finally, cholesterol added significantly to the predictive power when HDL-C and systolic blood pressure were already in the model.

Triglyceride levels [ln(Trig)] did not enter as a significant risk factor for raised lesions over and above that of the other lipid components. In the full regression model no risk factors other than cholesterol, HDL-C and systolic blood pressure contributed significantly to R^2, which remained unchanged when all other variables were added to these 3 factors. A search for interaction term for CHOL × SBP was negative and highly significant and that for SBP × HDL-C was of borderline significance (data not given). The R^2 was raised from 0.24 to 0.32 by the addition of CHOL × SBP in model 4.

The cholesterol ratio was also tested as an independent explanatory variable, but only gave somewhat increased explanatory power in relation to HDL-C alone, but not in relation to cholesterol and HDL-C when they were entered simultaneously as linear terms in the model (data not given).

Similar data for stenosis as the dependent variable are presented in Table V, given only for the Sten 1 variable. As with raised lesions, only cholesterol, HDL-C and systolic blood pressure were significant variables, with HDL-C and systolic blood pressure being less significant than serum cholesterol. Cigarette smoking was as poorly associated with stenosis as it was with raised lesions. No other variables even reached borderline significance. However, when the variable raised lesions was entered in the model, no risk factor was any longer significantly associated with stenosis. This was true whether adding 1 at a time, 2 at a time, or altogether, and this was consistent for all 3 stenosis variables (data not given).

One additional observation is that total and HDL-C tended to be more strongly associated with Sten 3 than with Sten 2, and again stronger with Sten 2 than with Sten 1, which is an indication that these risk factors become more important as predictors for the advanced stages of the stenosis process. The ordinal logistic regression, with Sten as dependent variable, assuming common regression coefficients for each factor across all stenosis groups, gave similar results, the only difference being that serum cholesterol increased its strength of association and systolic blood pressure became less significant (data not given).

Table VI is similar to the preceding tables, but involves CHD as the dependent variable. Again, exactly the same factors as mentioned above appeared as independent risk factors, that is, serum cholesterol, HDL-C and SBP, but SBP was less significant than before. None of the other variables entered into either the univariate or the multivariate analyses. Triglycerides appeared, however, as a factor of borderline significance in the multivariate analysis but with a negative

TABLE III Means, Standard Deviations and 0-Order Correlation Coefficients Between All Variables

Variable Name	n	Mean	SD	Correlation Coefficients														
				CHD	Sten 1	Sten 2	Sten 3	RL	Chol	HDL	Chol Ratio	ln(Trig)	SBP	DBP	Ciga-rettes	Social Class	Physical Activity at Leisure	Physical Activity at Work
CHD (0–1)	204	0.382	0.487	1.00	0.54	0.60	0.62	0.56	0.27	−0.33	−0.36	0.10	0.15	0.12	0.01	0.02	−0.03	−0.08
Sten 1 (0–1)	204	0.618	0.487		1.00	—	—	0.68	0.28	−0.19	−0.27	0.17	0.23	0.22	0.02	−0.06	0.08	−0.06
Sten 2 (0–1)	185	0.578	0.495			1.00	—	0.74	0.32	−0.23	−0.32	0.20	0.23	0.24	0.00	−0.06	0.08	−0.08
Sten 3 (0–1)	161	0.516	0.501				1.00	0.76	0.38	−0.26	−0.36	0.22	0.20	0.23	0.00	−0.07	0.09	−0.05
RL (%)	204	47.8	26.2					1.00	0.38	−0.33	−0.41	0.23	0.27	0.26	0.02	−0.08	0.02	−0.04
Chol (mg/dl)	204	288.6	46.6						1.00	−0.14	−0.48	0.42	0.10	0.11	0.10	−0.15	0.05	0.01
HDL (mg/dl)	177	31.4	11.0							1.00	0.92	−0.27	−0.01	−0.011	−0.04	−0.06	0.08	0.07
Chol ratio (HDL/Chol-HDL) × 100	177	12.9	5.9								1.00	−0.36	−0.04	−0.13	−0.06	0.04	0.03	0.08
Ln(Trig) (mmol/l)	204	0.833	0.447									1.00	0.03	0.06	0.09	−0.03	−0.01	0.04
SBP (mm Hg)	204	144.4	20.4										1.00	0.73	0.01	0.03	−0.07	0.02
DBP (mm Hg)	204	92.1	12.7											1.00	−0.03	0.04	−0.05	−0.04
Cigarettes (no./day)	204	10.5	8.7												1.00	0.19	−0.22	0.08
Social class (1–5)	204	3.85	0.77													1.00	−0.15	0.33
Physical activity at leisure (1–4)	203	1.86	0.65														1.00	−0.02
Physical activity at work (1–4)	196	1.92	0.90															1.00

CHD = coronary heart disease; Chol = cholesterol; DBP = diastolic blood pressure; HDL = high-density lipoprotein; ln(Trig) = triglycerides after transformation to natural logarithm; RL = raised lesions; SBP = systolic blood pressure; SD = standard deviation; Sten 1, 2, 3 = 3 stenosis variables.

TABLE IV Partial Regression Coefficients (β) and Their t Values for Coronary Raised Lesions in Relation to Coronary Risk Factors for 10 Selected Models with R^2 (n = 204; n = 177 When HDL is Included)

Model No.		R^2	Serum Cholesterol (mg/dl)	HDL Cholesterol (mg/dl)	ln (Trig) (mmol/l)	SBP (mm Hg)	Cigarette Smoking (no./day)	Social Class (1–5)	Physical Activity (1–4)	
									Work	Leisure
1	β	0.14	0.213				−0.065			
	t		5.8*				−0.33			
2	β	0.19	0.170	−0.67						
	t		4.3*	−4.1*						
3	β	0.19	0.199			0.294				
	t		5.6*			3.6*				
4	β	0.24	0.161	−0.66		0.262				
	t		4.2*	−4.2*		3.1†				
5	β	0.01					0.100	−3.11		
	t						0.47	−1.28		
6	β	0.15	0.191		5.29					
	t		4.7*		1.3					
7	β	0.19	0.162	−0.642	2.48					
	t		3.9*	−3.9*	0.56					
8	β	0.24	0.152	−0.642	2.51	0.262				
	t		3.7*	3.9*	0.58	3.1†				
9	β	0.16		−0.756		0.291				
	t			−4.6*		3.3*				
10	β	0.24	0.136	−0.595	3.96	0.290	−0.081	−2.46	−1.57	1.41
	t		3.1†	−3.5*	0.88	3.3†	−0.38	−0.98	−0.76	0.51

* $p < 0.001$; † $p < 0.01$.
Abbreviations as in Table III.

TABLE V Partial Logistic Regression Coefficients (β), Their Chi-Square Values and -2 ln(Likelihood) for Sten 1 in Relation to Coronary Risk Factors for 10 Selected Models (n = 204; n = 177 When High-Density Lipoprotein Cholesterol Included)

Model No.		Serum Cholesterol (mg/dl)	HDL Cholesterol (mg/dl)	ln (Trig) (mmol/l)	SBP (mm Hg)	Cigarette Smoking (no./day)	Social Class (1–5)	Physical Activity (1–4)		-2 lnL
								Work	Leisure	
1	β	0.014				−0.002				
	χ^2	15.2*				0.01				254.0
2	β	0.013	−0.032							
	χ^2	11.1*	4.4‡							209.4
3	β	0.013			0.023					
	χ^2	13.5*			8.1†					245.2
4	β	0.013	−0.033		0.022					
	χ^2	10.2†	4.7‡		6.0‡					202.8
5	β					0.009	0.183			
	χ^2					0.28	0.98			270.3
6	β	0.013		0.383						
	χ^2	11.0*		0.99						253.0
7	β	0.013	−0.029	0.26						
	χ^2	9.2†	3.6‡	0.35						209.1
8	β	0.013	−0.031	0.235	0.022					
	χ^2	8.5†	3.8‡	0.27	6.0‡					202.6
9	β		−0.038		0.023					
	χ^2		6.3‡		6.9†					214.1
10	β	0.011	−0.030	0.314	0.023	0.007	−0.218	−0.244	0.215	192.3
	χ^2	5.8‡	3.2‡	0.46	5.9‡	0.12	0.70	1.5	0.61	

* $p < 0.001$; † $p < 0.01$; ‡ $p < 0.1$.
Abbreviations as in Table III.

sign. If raised lesions or stenosis or both are forced into the model, HDL-C still appears as an inverse and significant risk factor working independently over and above that of all other factors (data not given). Figure 1 shows the association between percent CHD and HDL-C in 3 groups of raised lesions. The independent negative association is clearly indicated.

Both raised lesions and stenosis associate strongly with CHD, and each of them adds explanatory value to the other, with or without other risk factors present (data not given).

CHD is the endpoint most alike the endpoint used in clinical data with a living total cohort amenable for long-term follow-up. In most investigations, cigarette smoking is found to be highly and significantly associated with CHD incidence in prospective, population-based follow-up studies, and it has been especially stressed that the cigarette mediated risk of a CHD event increases as the severity (often measured by high levels of serum cholesterol or blood pressure or both) of atherosclerosis increases.[4,15] Therefore, the association between CHD and cigarette smoking has been explored

TABLE VI Partial Logistic Regression Coefficients (β), Their Chi-Square Values and -2 ln(Likelihood) for Coronary Heart Disease in Relation to Coronary Risk Factors for 10 Selected Models (n = 204; n = 177 When High-Density Lipoprotein Included)

Model No.		Serum Cholesterol (mg/dl)	HDL Cholesterol (mg/dl)	ln (Trig) (mmol/l)	SBP (mm Hg)	Cigarette Smoking (no./day)	Social Class (1–5)	Physical Activity (1–4) Work	Physical Activity (1–4) Leisure	-2 lnL
1	β	0.013				−0.005				255.9
	χ^2	14.0*				0.08				
2	β	0.009	−0.072							213.2
	χ^2	5.4‡	15.2*							
3	β	0.012			0.014					252.7
	χ^2	12.9*			3.3‡					
4	β	0.008	−0.071		0.0141					210.2
	χ^2	4.9‡	15.2*		2.9‡					
5	β					0.001	0.064			271.3
	χ^2					0.00	0.11			
6	β	0.013		−0.098						255.9
	χ^2	12.3†		0.07						
7	β	0.011	−0.077	−0.581						211.2
	χ^2	6.9†	16.6*	1.9						
8	β	0.010	−0.077	−0.569	0.014					208.4
	χ^2	6.4‡	16.7*	1.8	2.8‡					
9	β		−0.075		−0.015					215.3
	χ^2		17.2*		3.4‡					
10	β	0.012	−0.078	−0.510	0.012	−0.006	−0.005	−0.204	−0.089	196.1
	χ^2	7.4†	15.4*	1.3	2.0	0.08	0.00	0.98	0.11	

* $p < 0.001$; † $p < 0.01$; ‡ $p < 0.1$.
Abbreviations as in Table III.

in different strata of raised lesions or stenoses to see if a tendency toward such an association could be traced. Figure 2 gives this relation for 3 subgroups of raised lesions, and in no groups are there tendencies towards a positive association between cigarette smoking and CHD. There are similar results for subgroups of stenoses (data not given).

Discussion

All inferences drawn from an autopsy series are contingent on the fact that everyone has died. With the autopsy information available, one of the consequences is that if a risk factor for CHD has the same strength with regard to other causes of death, the analysis of autopsy series will show no association with such factors to CHD, but may well show it in a population-based follow-up study. Causes of death are also more strongly competing against each other in this age group than in the living population. These limitations of autopsy findings must be considered when discussing similarities and differences between clinical and autopsy-based epidemiologic risk factor analyses that use CHD as the endpoint.

The degree of atherosclerosis as measured by raised lesions in this total autopsy material, consisting of 471 cases, was 44% in nonattendants and 48% in attendants ($p > 0.10$). This indicates a small selection difference with respect to coronary risk in the autopsy series. For those who attended with risk factor levels available, nonautopsied cases had a slightly but not significantly ($p > 0.10$) lower risk profile than autopsied cases. The proportion of CHD death among all deaths in the cohort

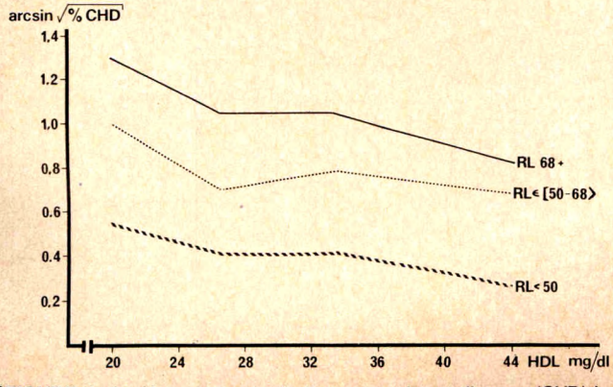

FIGURE 1. Arcsine square root of coronary heart disease (CHD) by high-density lipoprotein (HDL) cholesterol in 3 subgroups of coronary raised lesions (RL).

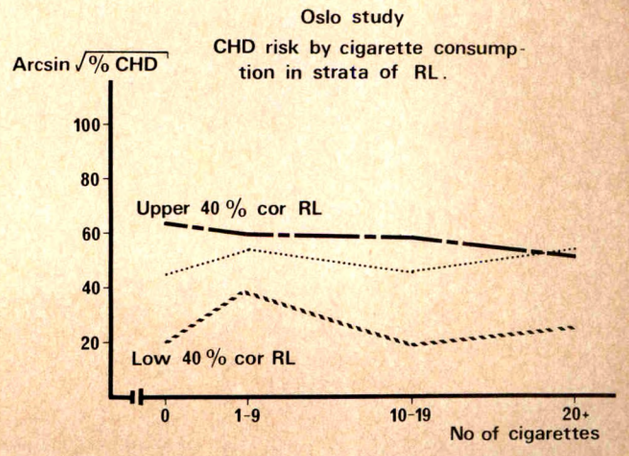

FIGURE 2. Arcsine square root × 100 of coronary heart disease (CHD) by cigarette smoking in 3 subgroups of coronary raised lesions (RL).

of all invited men to the Oslo Study was 36.4%, whereas in the autopsy series it was 38.2%. However, the CHD morbidity and mortality was 60% higher in the nonattending group than in the attending group during the first 5 years of follow-up.[5,16]

Serum cholesterol: The association between serum cholesterol and coronary raised lesions is highly significant both in univariate and multivariate analyses, as found in similar prospective autopsy studies among men.[17–20] The same association also applies for coronary stenosis, in univariate and in multivariate analyses, but when the variable raised lesions is entered into the multivariate model, serum cholesterol is no longer a significant risk factor. Analogously, serum cholesterol is also strongly associated with CHD death, both in univariate and in multivariate analyses, but when either raised lesions or stenosis are added to the model, serum cholesterol disappears as a risk factor. This finding is consistent with the hypothesis that cholesterol operates through establishment of raised lesions and by increasing the severity of stenosis and does not appear to influence other mechanisms of CHD death. These findings are in line with those from follow-up studies in the living population where serum cholesterol is a strong predictor for CHD morbidity and mortality.[5,16]

Blood pressure: The differences in associations between the dependent variables and the 2 blood pressure measurements were systematically small. With regard to raised lesions, systolic blood pressure was slightly more associated than diastolic, but for CHD diastolic blood pressure was somewhat more strongly associated. For stenosis the associations were of similar strength. Blood pressure was independently and significantly related to all 3 dependent variables, but most strongly to raised lesions. An association between blood pressure and raised lesions has been observed in some studies,[17,20] but not in others.[18,19] One reason why the association between blood pressure and CHD was only of borderline significance may be that blood pressure strongly relates to stroke which was included in the non-CHD death category, thus diluting the association. In addition, blood pressure seems to influence in a similar way CHD death as serum cholesterol, both being completely nonsignificant when raised lesions is entered into the models.

HDL cholesterol: This study is, to our knowledge, the first to demonstrate the systematic inverse relation between HDL-C and the 3 dependent variables both in univariate and multivariate analyses. This is more striking when it is realized that HDL-C measurements were done in frozen sera, with a reduction both in the mean and the dispersion by approximately 30%.[11] This finding is consistent with the clinical observation of HDL-C being an important acute atherogenic coronary risk factor[21–22] and supports the view that HDL-C may be operative at the formation level of atherosclerotic lesions. However, HDL-C was also a significant correlate to CHD, even after adjustments for raised lesions, stenosis and all the other independent variables. This result gives support to the theory that HDL-C may also influence other mechanisms that cause CHD death. A possible pathway of additional action would be through the association of HDL-C with factors that induce thrombi and spasm, but the literature is scarce with respect to a possible association between blood clotting factors and HDL-C. In the Oslo Study an inverse association between decreased fibrinolytic activity and triglycerides was shown,[23] but HDL-C was not evaluated in that study. The inverse association between triglycerides and HDL-C is well known,[24] so the question should be raised whether there exist associations between some blood clotting factors and HDL-C.

Another possible explanation is that HDL-C may be positively associated with alcohol consumption, which again could be negatively associated with CHD mortality in this population, but it is difficult to evaluate this explanation without alcohol consumption information, which was not available. However, 7 deaths were directly alcohol-related and these 7 men had a mean HDL-C level of 35.6 mg/dl (average 31.4).

Cigarette smoking: Cigarette smoking was not associated with any of the 3 dependent variables. For both raised lesions and stenosis, no tendency toward such an association was traced, either in univariate or in multivariate analyses, and this holds even within specific causes of death, such as cancer. Only the Honolulu study demonstrated an independent association between coronary raised lesions and cigarette smoking (restricting attention to prospective autopsy follow-up studies).[19] In neither the Malmo nor the Puerto Rico studies was such an association shown,[17,18] although for both studies a positive relation was shown between smoking and aortic atherosclerosis. This difference between the clinical and autopsy-based cigarette association to CHD could be explained by factors other than atherosclerotic lesions and stenoses. For instance, cigarette smoking may affect the myocardium and its conduction system,[25] it may interfere with the hematologic factors to enhance the formation of thrombi or spasm,[26] or cause fatal rhythm disturbances, thus more influencing complications to atherosclerosis. The relation between atherosclerosis in postmortem studies and cigarette smoking was recently reviewed.[27]

Clinical studies have shown that when atherosclerosis is advanced, cigarette smoking is an especially dangerous habit with respect to risk of CHD.[4,15] An attempt to investigate this hypothesis was made within this data set. When the data are grouped into 3 groups of raised lesions or in 4 groups of stenosis, one should expect the smoking factor to be negatively associated with CHD in the group of minor lesions or stenosis in which a predominance of non-CHD causes of death such as cancer is present. In the advanced raised lesions or stenosis group, however, the opposite should take place, with a clear positive tendency toward association between cigarette smoking and CHD. However, such a tendency could not be traced in these data where the lines of association were horizontal in all subgroups of raised lesions or stenosis (Fig. 2).

These findings are in contrast to what has been found in a similarly analyzed study of nonfatal myocardial infarction based on angiographically established coronary stenosis.[28] Also, selective biases may be present that tend to obscure the relation in the present data set.

Thus, the negative result for cigarette smoking in this study should be interpreted with care and can hardly be used as an argument against cigarette smoking as a deleterious factor in CHD.

Triglycerides: Triglyceride levels evaluated as ln(trig) was not a significant variable for raised lesions or stenosis in multivariate analysis. However, simple correlation coefficients of raised lesions and the 3 stenosis variables were technically significant ($p < 0.10$). With respect to raised lesions, this is in accordance with 1 study using univariate analysis,[19] but not with another.[18] Only the Honolulu study used multivariate analysis, and triglycerides did not appear to be significantly associated.[19] In the Oslo Study cohort follow-up, the triglyceride level was a significant positive risk factor for acute myocardial infarction even after adjustment for serum cholesterol.[15] This finding is not confirmed in the analysis of CHD against triglycerides in this study, even though the triglyceride level does not appear to be associated with other causes of death.

Social class and physical activity: Both social class and level of physical activity were far from being independent risk factors, even in univariate analyses. In the total cohort follow-up study, social class and physical activity at leisure were strongly related to CHD morbidity and mortality in univariate analysis. Physical activity at work was only of borderline significance (and was positively related to the outcome).[5,29] In a multivariate ecological analysis based on grouped data, only physical activity at leisure was of borderline significance for association with total mortality after adjustment for social class and coronary risk score (based on serum cholesterol, blood pressure and cigarette smoking).[29] Again, selection biases can not be ruled out as an explanation for the discrepancy with the clinical data.

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Percutaneous Transluminal Coronary Angioplasty After Intracoronary Streptokinase in Evolving Acute Myocardial Infarction

SILVIO E. PAPAPIETRO, MD, WILLIAM A. H. MacLEAN, MD, ALFRED W. H. STANLEY, Jr., MD, RANDALL G. HESS, DO, NAN CORLEY, MD, JOAQUIN G. ARCINIEGAS, MD, and TERRY B. COOPER, MD

To achieve optimal myocardial revascularization and prevent rethrombosis of the infarct-related coronary artery, percutaneous transluminal coronary angioplasty (PTCA) was attempted in 18 patients with evolving acute myocardial infarction (9 anterior and 9 inferior) after administration of intracoronary streptokinase. PTCA was attempted 338 ± 151 minutes after the onset of symptoms. After thrombolytic therapy, 11 patients had a severe residual stenosis and 7 a persistent total occlusion of the infarct-related coronary artery. PTCA was successful in 13 of 18 patients: in 9 of 11 with coronary stenoses and in 4 of 7 with total coronary occlusions. PTCA reduced the severity of the coronary lesion from 91 ± 2% to 27 ± 7% ($p < 0.001$), and the transstenotic pressure gradient from 38 ± 5 to 6 ± 2 mm Hg ($p < 0.01$). One patient in cardiogenic shock died during urgent coronary surgery after unsuccessful PTCA. After PTCA, all patients received heparin and antiplatelet agents. One patient had reinfarction with reocclusion of the infarct-related artery 5 days after PTCA. The other 12 patients had an uneventful hospital course, and cardiac catheterization before hospital discharge (8 to 17 days) revealed reocclusion of the infarct-related coronary artery in 3 and persistent patency in 9. Persistent patency of the infarct-related artery was associated with preservation of left ventricular end-diastolic volume (initial 86 ± 6 ml/m², follow-up 91 ± 6 ml/m²), and improvement in left ventricular ejection fraction in some patients.

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Thrombolysis with streptokinase (STK) early after the onset of acute myocardial infarction (AMI) frequently results in reestablishment of blood flow in thrombosed coronary arteries.[1–3] After thrombolysis, residual stenoses usually remain at the site of initial occlusion, and may result in incomplete revascularization and rethrombosis.[2,4,5] Anticoagulant and antiplatelet agents have been used to prevent rethrombosis, with variable success.[2–5] Coronary artery bypass surgery and percutaneous transluminal coronary angioplasty (PTCA) have been used immediately after or several days after thrombolysis to prevent reocclusion and achieve complete revascularization.[2–4] In this study, we report our experience with 18 patients with evolving transmural AMI in whom PTCA was attempted immediately after intracoronary STK treatment.

From the Division of Cardiology, Department of Medicine, Carraway Methodist Medical Center, and Norwood Clinic, Birmingham, Alabama. This study was supported by the Kemp-Carraway Heart Institute, Birmingham, Alabama. Manuscript received June 18, 1984; revised manuscript received August 29, 1984, accepted August 31, 1984.

Address for reprints: Silvio E. Papapietro, MD, Division of Cardiology, Carraway Methodist Medical Center, 1600 North 26th Street, Birmingham, Alabama 35234.

Methods

Patients: From October 1981, through December 1982, 83 patients with an evolving transmural AMI underwent cardiac catheterization and received intracoronary STK within 12 hours from onset of symptoms. The diagnosis of AMI was established by a history of chest pain, associated with more than 1.5 mm of ST-segment elevation in 2 or more electrocardiographic leads. Patients gave informed consent for cardiac catheterization, thrombolysis and PTCA. After administration of intracoronary STK, 18 patients (Table I) were selected for PTCA. They represent consecutive PTCA attempts, and were considered candidates for PTCA because after STK, they had a persistent occlusion or a severe stenosis in the infarct-related artery, jeopardizing a large segment of myocardium. The coronary lesion was believed suitable for

TABLE I Clinical Characteristics of Patients

Pt	Age (yr) & Sex	Previous MI	Location of AMI	Initial LVEDP (mm Hg)	Initial CI (l/min/m²)	Time from Onset of Symptoms to PTCA (min)	Extent of CAD
1	43M	No 0	Inf	15	1.85	350	1V
2	50M	No 0	Inf	20	3.29	185	1V
3	57M	No 0	Ant	30	2.73	135	2V
4	63F	No 0	Inf	20	2.57	502	3V
5	67F	No 0	Ant	27	1.85	304	2V
6	41M	No 0	Inf	18	3.63	508	3V
7	54F	No 0	Ant	35	3.75	245	2V
8	54F	No 0	Inf	16	3.12	341	2V
9	71M	No 0	Ant	8	2.20	755	3V
10	46M	No 0	Inf	19	3.27	285	1V
11	55M	No 0	Ant	46	3.20	427	1V
12	33M	No 0	Inf	15	3.96	413	1V
13	62M	No 0	Ant	30	2.18	127	1V
14	37M	No 0	Inf	20	. . .	265	1V
15	49M	No 0	Ant	15	3.37	389	1V
16	45M	No 0	Ant	32	3.37	210	1V
17	46M	Yes +	Inf	20	2.56	215	2V
18	59M	No 0	Ant	30	3.39	419	1V

AMI = acute myocardial infarction; Ant = anterior; CAD = coronary artery disease; CI = cardiac index; Inf = inferior; LVEDP = left ventricular end-diastolic pressure; PTCA = percutaneous transluminal coronary angioplasty; V = vessel; + = present; 0 = absent.

PTCA based on its proximity to the ostium of the artery, type (discrete, concentric, noncalcified), presence and extent of residual thrombus and experience of the operator.

Cardiac catheterization: After initial evaluation, the 18 patients underwent cardiac catheterization (femoral approach). Cardiac output was determined by thermodilution. Biplane left ventricular angiography (30° right anterior oblique/15° cranial–60° left anterior oblique) was performed using 36 ml of diatrizoate meglumine injected over 3 seconds. Coronary angiography was performed in multiple views, and was performed first in the artery suspected not to be responsible for the AMI. Complete occlusion of the infarct-related artery was found in 16 patients and severe subtotal occlusion with nonocclusive thrombus was found in 2 (Table II).

Streptokinase: Patients received heparin, 10,000 IU, diphenhydramine hydrochloride, 50 mg, and methylprednisolone, 1.0 g intravenously, and nitroglycerin, 100 to 250 μg into the ostium of the infarct-related artery (left main or right coronary artery). No improvement in flow was observed after nitroglycerin. Subsequently, STK (Streptase,® Hoechst) 250,000 IU in 250 ml of 0.9 *M* sodium chloride, was administered as a 20,000-IU bolus in the infarct-related artery, and followed by an infusion of 4,000 or 8,000 IU/min, until the artery was recanalized or to a maximum of 400,000 IU. Coronary arteriograms were performed at regular intervals during STK administration. Recanalization was considered successful if flow was reestablished in a totally occluded vessel, or improved and the initial stenosis reduced in a subtotally occluded vessel. STK recanalization was successful in 9 patients with total occlusions and in the 2 with subtotal occlusions. In 7 patients STK recanalization was unsuccessful.

Angioplasty: Immediately after STK, PTCA[6] was attempted in the 18 patients. Movable guidewire angioplasty systems were not used. The mean time from onset of symptoms of AMI to PTCA was 338 ± 151 minutes (± standard deviation) (Table I). PTCA was considered successful when it resulted in recanalization and reestablishment of flow in a totally occluded artery, or an increase of more than 30% in the diameter of the lumen in a partially occluded artery. PTCA was attempted only in the infarct-related artery.

Management and follow-up: After PTCA, a No. 9Fr arterial sheath was left in the femoral artery for 12 to 16 hours while the patients were monitored in the coronary unit. Heparin, 1,000 to 1,500 IU/hour, was continuously infused to maintain the partial thromboplastin time 2 to 2½ times control for 3 to 5 days. All patients received dipyridamole or aspirin at least until follow-up cardiac catheterization. Oral anticoagulant treatment was not used routinely. Nitrates, calcium and β-blocking agents were used at the discretion of the attending physician. All patients with successful PTCA underwent follow-up cardiac catheterization before hospital discharge. Left ventricular volumes were derived from biplane left ventriculography.[7,8]

Statistical analysis: Data are reported as percentages and mean ± standard error of the mean. The significance of difference was assessed by paired *t* test (continuous variables) and by analysis of covariance (improvement in ejection fraction as dependent variable and collateral vessels time to reperfusion and late patency of the infarct artery as independent variables).

Results

Success and failure: PTCA was successful in 13 of 18 patients (72%): in 9 of 11 with a residual stenosis after thrombolytic therapy, and in 4 of 7 with persistent total coronary occlusions.

In the 4 patients with totally occluded arteries in whom PTCA was successful, the dilatation catheter was advanced through the occlusion site and anterograde flow documented by injection of contrast media. The balloon was usually inflated several times at this site until no significant transstenotic pressure gradient (mean less than 15 mm Hg) was present.

In the 13 patients with successful PTCA, the degree of coronary artery obstruction was reduced from 91 ± 2% to 27 ± 7% ($p < 0.001$) and the mean transstenotic pressure gradient from 38 ± 5 to 6 ± 2 mm Hg ($p < 0.01$). Figures 1 and 2 illustrate successful PTCA in 2 patients.

PTCA was unsuccessful in 5 of 18 patients (28%): in 3 patients a total occlusion could not be crossed and in 2 with residual stenoses it was associated with complications.

TABLE II Catheterization and Follow-Up Data

	Initial							Post STK		Post PTCA	Follow-up			
Pt	EDV (ml/m²)	ESV (ml/m²)	EF	MI-CA	Initial MI-CA Stenosis (%)	Collat. to MI-CA		MI-CA Stenosis (%)	PTCA	MI-CA Stenosis (%)	EDV (ml/m²)	ESV (ml/m²)	EF	MI-CA Stenosis (%)
1	118	56	0.52	RCA	100	+		95	S	20	115	49	0.57	30
2	86	45	0.48	RCA	100	+		85	S	0	83	29	0.65	0
3	149	94	0.37	LAD	100	0		90	S	40	160	99	0.38	100
4	58	29	0.51	RCA	100	+		90	S	0	67	27	0.61	20
5	77	52	0.33	LAD	100	0		90	U	90				
6	66	27	0.60	RCA	100	0		95	U	100				
7	93	57	0.39	LAD	100	0		95	S	65	93	56	0.40	50
8	85	37	0.57	RCA	100	0		90	S	10	86	29	0.66	10
9	61	45	0.45	LAD	90			80	S	20	95	58	0.39	60
10	100	35	0.66	RCA	100	0		80	S	30	84	27	0.68	100
11	95	52	0.45	LAD	100	+		100	S	0	93	45	0.52	0
12	91	41	0.55	RCA	100	0		100	S	60	124	66	0.46	55
13	72	31	0.57	LAD	100	0		100	U	100				
14	95	34	0.65	RCA	90			80	S	50	68	30	0.55	50
15	117	45	0.62	LAD	100	0		100	U	100				
16	100	59	0.42	LAD	100	0		100	U	100				
17	84	38	0.56	RCA	100	+		100	S	40	93	50	0.47	100
18	100	58	0.43	LAD	100	+		100	S	40	89	48	0.46	100

Collat. = collateral vessels; EDV = left ventricular end-diastolic volume; EF = left ventricular ejection fraction; ESV = left ventricular end-systolic volume; LAD = left anterior descending coronary artery; MI-CA = infarct-related coronary artery; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; S = successful; STK = streptokinase; U = unsuccessful; + = present; 0 = absent.

Complications and mortality: Two patients had complications related to PTCA. The first complication developed in a woman with an evolving anterolateral AMI (patient 5) associated right bundle branch block, recurrent ventricular tachycardia, and shock. After thrombolytic recanalization of the totally occluded left anterior descending artery, and as the dilatation catheter was being advanced across a residual 90% stenosis in the midsegment of the artery, ventricular fibrillation developed. Electrical cardioversion restored sinus rhythm and vital signs. Angiograms revealed patency of the artery, with no change in the midsegment stenosis and slow distal flow. The procedure was terminated, and urgent coronary bypass surgery was performed. The patient died in the operating room. She represents the only in-hospital death (1 of 18 patients or [5.5%]). The second complication occurred in a man with an evolving inferior AMI (patient 6) in whom the right coronary artery was recanalized with STK, leaving a severe 95% proximal stenosis. PTCA resulted in dissection and reocclusion of the right coronary artery. The patient had an otherwise uncomplicated hospital course.

Hospital course and follow-up: Hemorrhagic complications occurred in 5 patients. Two had recurrent bleeding with hematoma formation at the femoral puncture site, 1 had upper gastrointestinal bleeding, 1 had flank pain and hematuria, and 1 had a fall in hematocrit level during treatment with heparin. In all patients, bleeding resolved without consequences after heparin administration was discontinued.

Patient 3 had anterolateral reinfarction 5 days after successful PTCA of the left anterior descending coronary artery. Cardiac catheterization revealed reocclusion of the artery, and urgent coronary bypass surgery was performed without complication.

The remaining 12 patients with successful PTCA had a stable and uneventful hospital course and underwent follow-up cardiac catheterization and angiography at a mean of 12 days (range 8 to 17). The infarct-related artery was patent in 9 (75%). In these 9 patients, the residual stenosis present immediately after PTCA (25 ± 8%) was unchanged at follow-up study (31 ± 8%, difference not significant [NS]). Left ventricular angiography revealed no changes in left ventricular end-diastolic volume (initial 86 ± 6 ml/m², follow-up 91 ± 6 ml/m², NS), while left ventricular ejection fraction increased (>0.04) in 5, decreased (>0.04) in 3 and was unchanged in 1 patient. An increase in ejection fraction was always associated with an improvement in wall motion in the infarct zone. The 4 patients in whom left ventricular ejection fraction did not increase (patients 7, 9, 12 and 14) were receiving β-blocking agents at the time of follow-up cardiac catheterization. Compared with patients in whom left ventricular ejection fraction did not improve, those in whom it increased more frequently had collateral vessels to the distal portion of the occluded infarct-related artery ($p = 0.04$), a shorter time from onset of symptoms to PTCA ($p = 0.15$), and a patent infarct-related artery at follow-up angiography ($p = 0.04$).

In 3 patients (25%) the infarct-related artery had reoccluded. Review of the hospital course in these 3

patients (nos. 10, 17 and 18) did not reveal a clinical event (chest pain, ST-segment changes during electrocardiographic monitoring, frequent or sustained ventricular arrhythmias or paroxysmal dyspnea) that could have been temporally associated to rethrombosis.

Discussion

In patients with evolving AMI, thrombotic occlusion of the infarct-related artery is frequently demonstrated if angiographic studies are performed soon after the onset of symptoms.[9] Intracoronary STK can recanalize the occluded artery in 60 to 90% of patients.[2–4,10,11]

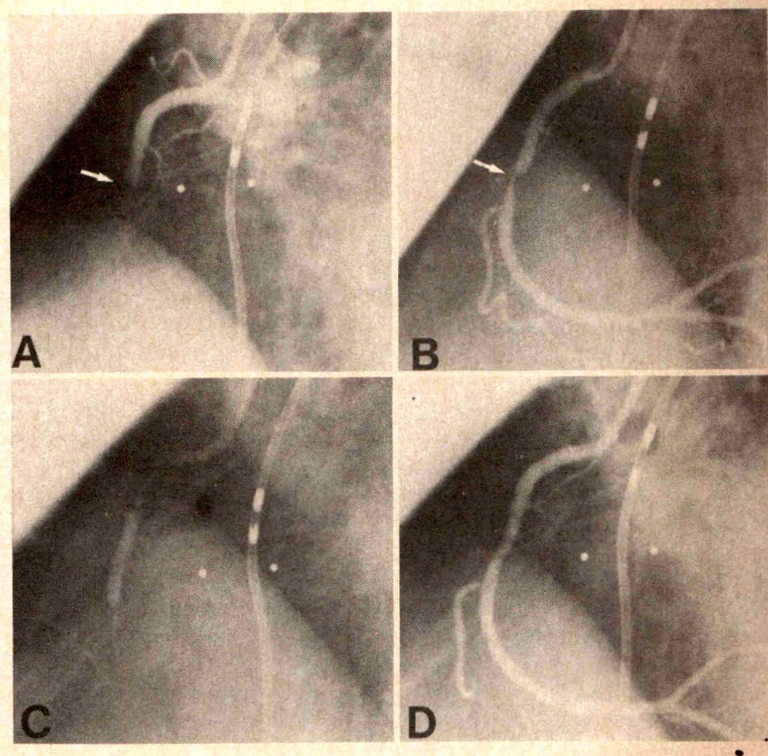

FIGURE 1. Right coronary angiograms (caudocranial left anterior oblique projection) in patient 2, in whom an inferior acute myocardial infarction was evolving. **A,** the right coronary artery is totally occluded in the midsegment (**arrow**). **B,** after recanalization with streptokinase, a severe residual stenosis (**arrow**) is present. **C,** the balloon dilatation catheter has been advanced and is inflated at the site of stenosis. **D,** after angioplasty, the right coronary artery has no residual stenosis.

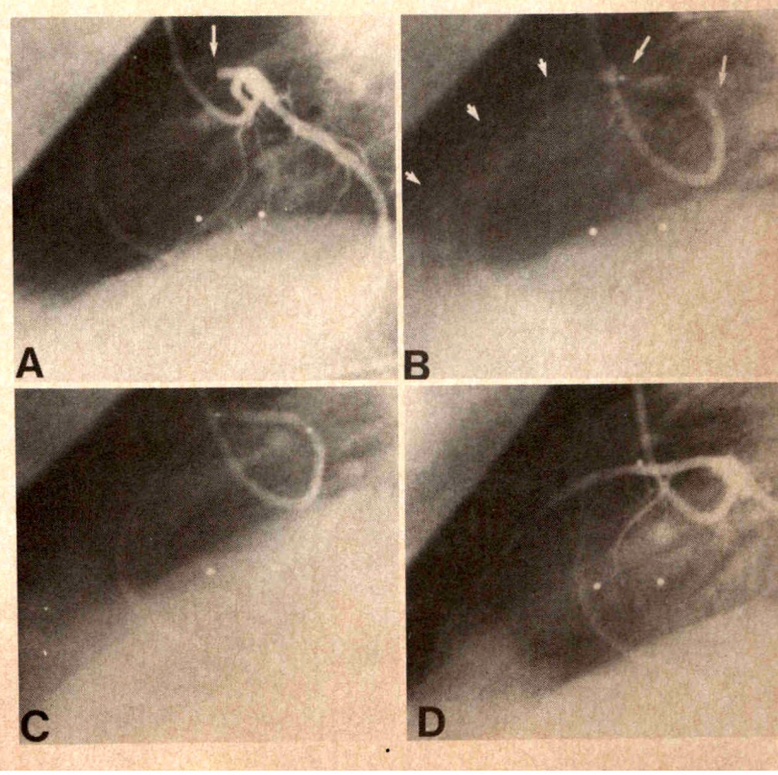

FIGURE 2. Left coronary angiograms (left lateral projection) in patient 11, in whom an anterior acute myocardial infarction was evolving. **A,** the left anterior descending artery is totally occluded in the proximal segment (**arrow**), after unsuccessful administration of streptokinase. **B,** the 2 radiopaque markers (**long arrows**) identify the position of the balloon dilatation catheter, which has been advanced through the occlusion site. The distal portion of the left anterior descending artery is faintly visualized (**short arrows**) with contrast medium injected through the balloon dilatation catheter. **C,** the balloon dilatation catheter is inflated at the site of occlusion. **D,** after angioplasty, no residual stenosis is present.

High-grade stenoses usually remain at the site of the thrombotic occlusion, and may prevent complete revascularization, or result in rethrombosis.[2,4,5] Reocclusion has been reported in 5 to 32% of patients undergoing angiography 7 days to 11 months after thrombolysis.[2–4,12] Furthermore, patients frequently have angina and eventually require surgery or PTCA.[2–4] Thus, PTCA immediately after thrombolysis may be an attractive option to prevent reocclusion and revascularize selected patients with AMI. However, the potential benefits of PTCA should outweigh the risks of the procedure in acutely ill patients, who are frequently hemodynamically unstable, and with a lytic state from STK.[11]

We attempted PTCA immediately after intracoronary STK treatment in a selected group of patients with evolving AMI. PTCA was successful in most patients with residual coronary stenoses, and in some with persistent total coronary occlusions. Follow-up cardiac catheterization, performed in all patients with successful PTCA, revealed persistent patency of the infarct-related artery in most patients, and this was associated with preservation of the initial left ventricular end-diastolic volume. However, 4 of 13 patients (31%) had early reocclusion of the infarct-related artery, which was silent and not associated with a new clinical event in (23%). Complications occurred infrequently, and were associated with a low mortality rate (1 of 18, 5.5%).

In this study, PTCA was successful in 72% of patients, a success rate similar to that of elective PTCA performed in patients with more stable coronary disease, not with evolving AMI.[13,14] We dilated 4 totally occluded arteries. The ability of PTCA to recanalize a totally occluded artery has been reported,[15] and represents a unique therapeutic option in selected patients with AMI in whom thrombolysis is contraindicated or has failed to restore blood flow. New movable guidewire PTCA systems may result in higher success and lower complication rates.[15]

Reocclusion after angioplasty: Four of 13 patients (31%) with successful PTCA of the infarct-related artery had reocclusion of the vessel, demonstrated by angiography before hospital dicharge. One patient (no. 3) had reinfarction with angiographic confirmation of rethrombosis. The other 3 (patients 10, 17 and 18) had clinically silent reocclusions. Although our patient population was small, these findings suggest that a successful PTCA may not prevent rethrombosis, and a clinically uneventful hospital course does not exclude reocclusion. The rethrombosis rate probably could have been reduced by more aggressive anticoagulation. However, it was not our purpose to evaluate the benefits of anticoagulation, but rather the ability of PTCA to prevent thrombotic reocclusion of the infarct-related artery. Thus, despite these limitations, the observation that a successful PTCA does not necessarily prevent rethrombosis is important and should have relevant clinical implications when evaluating therapeutic options in patients with AMI. The relatively high rate of reocclusion observed in our patients could be related to compression and molding of thrombi against the arterial wall, which may propagate and result in reocclusion. Whether additional administration of STK after PTCA, or more aggressive heparin therapy would result in a lower rethrombosis rate is not known.

Left ventricular function after angioplasty: Patients in whom the infarct-related artery remained patent after PTCA had no changes in left ventricular end-diastolic volume. This was associated with a reduction in end-systolic volume and an increase in ejection fraction in those not receiving β-blocking drugs at follow-up angiography. After AMI treated conventionally, there is progressive left ventricular dilatation in proportion to the size of the infarction.[16–19] Thus, the absence of left ventricular dilatation associated with persistent patency of the infarct-related artery probably reflects a reduction of infarct size and preservation of ventricular myocardium.

Hospital mortality: One critically ill patient died during urgent coronary bypass surgery after unsuccessful PTCA. Our population was nonrandomized, selected and too small to allow us to draw conclusions concerning hospital mortality from PTCA during AMI. However, several patients had reduced cardiac index, elevated left ventricular filling pressure, and reduced ejection fraction, variables associated with a high mortality rate in AMI.[20,21] Thus, a mortality rate of 5.5% compares favorably with that observed when more conventional modalities of treatment are used.[22]

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Positive Exercise Thallium-201 Test Responses in Patients with Less Than 50% Maximal Coronary Stenosis: Angiographic and Clinical Predictors

KENNETH A. BROWN, MD, MARY OSBAKKEN, MD, CHARLES A. BOUCHER, MD, H. WILLIAM STRAUSS, MD, GERALD M. POHOST, MD, and ROBERT D. OKADA, MD

The incidence and causes of abnormal thallium-201 (Tl-201) myocardial perfusion studies in the absence of significant coronary artery disease were examined. The study group consisted of 100 consecutive patients undergoing exercise Tl-201 testing and coronary angiography who were found to have maximal coronary artery diameter narrowing of less than 50%. Maximal coronary stenosis ranged from 0 to 40%. The independent and relative influences of patient clinical, exercise and angiographic data were assessed by logistic regression analysis. Significant predictors of a positive stress Tl-201 test result were: (1) percent maximal coronary stenosis ($p < 0.0005$), (2) propranolol use ($p < 0.01$), (3) interaction of propranolol use and percent maximal stenosis ($p < 0.005$), and (4) stress-induced chest pain ($p = 0.05$). No other patient variable had a significant influence. Positive Tl-201 test results were more common in patients with 21 to 40% maximal stenosis (59%) than in patients with 0 to 20% maximal stenosis (27%) ($p < 0.01$). Among patients with 21 to 40% stenosis, a positive test response was more common when 85% of maximal predicted heart rate was achieved (75%) than when it was not (40%) ($p < 0.05$). Of 16 nonapical perfusion defects seen in patients with 21 to 40% maximal stenosis, 14 were in the territory that corresponded with such a coronary stenosis. Patients taking propranolol were more likely to have a positive Tl-201 test result (45%) than patients not taking propranolol (22%) ($p < 0.05$). Although patients with stress-induced chest pain more often had a positive Tl-201 test result than those without chest pain, this difference did not reach statistical significance. However, Tl-201 perfusion defects were more frequently seen when typical angina pectoris was elicited than when atypical chest pain developed ($p < 0.05$). The high frequency of Tl-201 defects associated with 21 to 40% stenoses and the close correlation of such defects with myocardial territory supplied by these stenoses suggests that such coronary lesions may have true hemodynamic impact, especially at high levels of stress. In addition, the high incidence of positive Tl-201 studies in patients taking propranolol suggests that an attempt be made to wean patients off β-blocker treatment before Tl-201 exercise testing.

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Thallium-201 (Tl-201) imaging with injection at exercise is a relatively specific procedure for the detection of myocardial ischemia and scar.[1,2] However, many investigators have observed abnormal Tl-201 responses in patients with noncritical coronary artery disease (CAD). In some cases, the abnormal scans can be attributed to causes other than myocardial ischemia, such as overlying breast tissue or an unusually high gastric fundus. Attenuation due to breast or stomach can frequently be appreciated at the time of image collection and can be corrected by recording additional views. However, even after considering these causes, there remain a group of patients who have definite abnormalities on their Tl-201 scans in the absence of angiographically critical coronary stenoses. To determine the role of the degree of subcritical coronary arterial narrowing and other factors on the incidence of positive Tl-201 scans, 100 consecutive patients with maximal coronary stenosis of less than 50% and who underwent

From the Cardiac and Nuclear Medicine Section, Departments of Medicine and Radiology, Massachusetts General Hospital, Boston, Massachusetts. This study was supported in part by U.S. Public Health Service grants HL 21751 and HL 26215 and by Cardiovascular Nuclear Medicine training grant HL 07416 of the National Institutes of Health, Bethesda, Maryland. Manuscript received August 29, 1983; revised manuscript received September 4, 1984, accepted September 6, 1984.

Address for reprints: Kenneth A. Brown, MD, Cardiology Unit, University of Vermont College of Medicine, Burlington, Vermont 05405.

Tl-201 stress testing were identified and form the basis of this report.

Methods

Patients: The study included 100 consecutive patients (Table I) undergoing both coronary angiography and exercise Tl-201 myocardial imaging for the evaluation of chest pain who were found to have a maximal coronary stenosis of less than 50% diameter narrowing. The range of maximal coronary stenosis was 0 to 40%. Patients were separated into 2 groups: 22 patients with a maximal coronary artery stenosis of 21 to 40% and 78 patients with a maximal stenosis of 0 to 20%, of whom 74 had normal angiograms. Five patients had 21 to 40% maximal stenoses in more than 1 coronary artery (3 two-vessel CAD and 2 three-vessel CAD). Radionuclide imaging and coronary angiography were performed within 2 weeks of each other; the radionuclide study was performed as part of a research protocol and was unrelated to the clinical decision to undergo catheterization. Propranolol was not discontinued for the study. No patient had clinical, radiographic or catheterization evidence of congestive heart failure, valvular disease or congenital heart disease. No patient had historical or electrocardiographic evidence of previous myocardial infarction.

Exercise protocol: Patients exercised either upright on a treadmill according to the standard Bruce protocol (66 patients) or in the supine position using a bicycle ergometer (34 patients). A 12-lead electrocardiogram, heart rate and blood pressure were recorded at rest and at each minute of exercise. For bicycle ergometry the initial workload was 25 W (150 kpm/min), and the workload was increased by 25 W every 3 minutes until fatigue developed. At peak exercise, 1.5 mCi of Tl-201 (New England Nuclear) was injected intravenously and the patient was encouraged to continue exercising for 45 seconds longer. A positive ischemic electrocardiographic response was defined as 1 mm of horizontal or downsloping ST-segment depression. Chest pain elicited during the stress test was recorded and classified as typical or atypical of angina pectoris. Typical angina included pain in the anterior thorax occurring during stress or immediately after exercise that was relieved with rest or nitroglycerin. Atypical angina lacked 1 or more of these features.

Image acquisition: Imaging was performed in the supine position in all patients using an Anger-type gamma camera (Picker Dynacamera, Picker Corp.) equipped with an all-purpose, low-energy, parallel-hole collimator and interfaced to a portable cardiac imaging computer (MUGA-CART, Medical Data Systems). Images were acquired using a 68 to 80-keV window encompassing the mercury x-ray peak of Tl-201. Imaging began with 5 minutes of cessation of exercise in all patients. Six-minute acquisitions were performed in the anterior and 45° left anterior oblique projections. Delayed views in the same projections were obtained 2 to 4 hours later.

Image analysis: Studies were interpreted along with 100 Tl-201 studies in patients with significant (≥50% stenosis) angiographic CAD. All observers were blinded to clinical and angiographic data. Qualitative interpretation of myocardial images was performed from computer-displayed, non-background-subtracted images by 3 experienced observers using previously defined averaged score criteria.[3] Briefly, each image was separated into 3 segments and each segment was scored as either 2 (normal), 1 (reduced activity) or 0 (absent activity). Half-grade scores were allowed for segments with slightly reduced activity (1.5) or nearly absent activity (0.5). Scores for each segment from the 3 observers were averaged and were interpreted as follows: a transient defect was present if a segment's average score on initial image was less than 1.5 and increased by 0.5 or more; a persistent defect was present if the average score on the initial image was less than 1.5 and did not increase by 0.5; a segment was normal if the average score on initial view was 1.5 or more. The presence of either a transient or persistent defect was considered a positive test response for CAD. These criteria have been previously shown to be associated with a high sensitivity and specificity for CAD compared with other qualitative scoring systems.[3]

To assess the correlation of myocardial perfusion defects to territory at risk, the inferior segment was assumed to be supplied by the right coronary artery, the septum and anterior segment by the left anterior descending artery, and the posterior wall by the left circumflex artery. Apical and apicoinferior segments were not assigned coronary territories.

Coronary angiographic data analysis: Coronary angiograms were interpreted by consensus by 2 experienced observers unaware of the patients' history and Tl-201 results. Maximal coronary stenosis was defined by maximal luminal diameter narrowing present in at least 2 projections.

Statistical analysis: Patient data are presented as mean ± standard deviation. A logistic regression analysis (BMDPLR, Health Service Computing Facility, University of California, Los Angeles, CA) was performed to assess the independent relative influence of various patient historical, exercise and angiographic data on positive Tl-201 test results. By this analysis, each variable is initially ranked by its chi-square value. The variable with the highest significant chi-square is entered into the logistic regression model and removed from the list. The process is then repeated stepwise until no significant variable is found. By this analysis, $p < 0.1$ is considered significant.

TABLE I Patient Characteristics

	Upright Exercise (n = 66)	Supine Exercise (n = 34)	p Value
Male:female	36:30	19:15	NS
Propranolol	26	19	NS
≥85% MPHR	37	14	NS
Ischemia on stress ECG	14	4	NS
Stress-induced chest pain	12	4	NS
Maximal stenosis 21–40%	17	10	NS
Maximal stenosis 0–20%	49	24	NS

ECG = electrocardiogram; MPHR = maximal predicted heart rate; NS = not significant.

Results

Patient characteristics: Clinical and exercise data are depicted in Table I. There was no significant difference in any patient parameter for upright compared to supine exercise.

Thallium-201 imaging data: Positive Tl-201 studies were seen in 34 patients. To assess the independent relative influence of method of exercise and the patients' clinical, exercise and angiographic data on the presence of Tl-201 perfusion defects, multiple-step logistic regression analysis was performed. On the initial ranking of patient variables, percent maximal stenosis had the greatest chi-square value and was entered into the logistic regression model. Subsequent analysis steps placed stress-induced chest pain, propranolol use and the interaction of percent maximal stenosis and propranolol use into the model. No other patient variable, including method of exercise (upright vs supine), was found to have significant influence. The significant predictive

TABLE II Significant Predictors of Positive Thallium-201 Test Result

	χ^2	p Value	r
% maximal stenosis	12.69	<0.0005	0.079
Interaction of maximal stenosis and propranolol use	8.32	<0.005	−0.088
Propranolol use	7.42	<0.01	1.39
Stress-induced chest pain	3.77	0.05	1.98
Constant			−1.90

variables and their chi-square, p values and coefficients are shown in Table II.

Positive Tl-201 test results were more common in patients with 21 to 40% maximal stenosis (13 of 22, 59%) than in patients with 20% or less maximal stenosis (21 of 78, 27%; p <0.01) (Fig. 1). Among patients with 21 to 40% stenosis, a positive test result was more common when 85% maximal predicted heart rate was achieved (9 of 12, 75%) than when it was not (4 of 10, 40%; p <0.05). Twenty-two defects were seen among the patients with 21 to 40% maximal stenosis. Of the 16 nonapical defects, 14 (88%) correspond to the territory of a 21 to 40% coronary stenosis.

Patients taking propranolol were more likely to have a positive Tl-201 test response (19 of 42, 45%) than patients not taking propranolol (13 of 58, 22%) (p <0.05) (Fig. 1). Patients with stress-induced chest pain more commonly had a positive Tl-201 test response (8 of 16, 50%) than patients without chest pain (26 of 84, 31%) but this did not reach statistical significance. However, Tl-201 perfusion defects were significantly more common when typical angina pectoris was induced during the stress test (6 of 8, 75%) than when atypical chest pain developed (2 of 8, 25%) (p <0.05).

Discussion

The present study demonstrates that Tl-201 perfusion defects during exercise in patients with maximal coronary stenosis of less than 50% is related to 3 independent factors: maximal coronary artery stenosis, propranolol use, and exercise-induced chest pain.

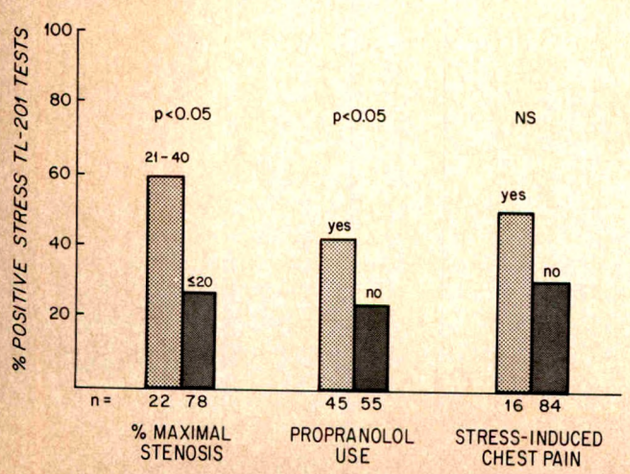

FIGURE 1. Frequency of positive exercise thallium-201 test responses as a function of the 3 significant logistic regression predictors. NS = not significant.

Maximal coronary artery stenosis: Percent maximal coronary artery stenosis was the most important predictor of a positive Tl-201 test response in this patient population. Patients with maximal stenosis of 21 to 40% more often had Tl-201 perfusion defects than patients with maximal stenosis of 20% or less. Although the luminal diameter of a coronary artery must be decreased by approximately 85% to reduce coronary blood flow at rest,[4] stenoses of 50% have been shown to prevent the usual hyperemic response to transient occlusion,[4] and may have hemodynamic significance during stress conditions. Isolated coronary stenoses of less than 50% have conventionally been assumed to be of no clinical importance. However, xenon-133 washout studies have revealed regional reductions in coronary perfusion associated with such lesions.[5] In addition, the usual angiographic grading of a coronary stenosis by its maximal luminal narrowing ignores the possible effect of the length of the lesion[6] and the effect of multiple obstructions of less than 50% within the same vessel.[7] Furthermore, the visual interpretation of coronary angiograms involves considerable inter- and intraobserver variance[8–10] and may lead to difficulty in distinguishing a stenosis of less than 50% from a stenosis greater than 50%. Finally, recent data suggest that visual interpretation of coronary angiographic lesions is a poor predictor of the physiologic importance of coronary stenoses assessed by hyperemic response to temporary occlusion.[11] For these reasons, angiography may underestimate the true hemodynamic impact of lesions that appear to be narrowed by less than 50% in luminal diameter.

Therefore, the segmental defects in Tl-201 uptake during exercise observed in 59% of patients with 21 to 40% coronary stenosis may well reflect a true regional reduction in myocardial blood flow. This is supported by the finding that Tl-201 defects in patients with 21 to 40% stenoses corresponded well to the myocardial territory supplied by such stenoses. In addition, Tl-201 defects in this group of patients were far more common when patients exercised to 85% maximal heart rate (75%) than when lower stress was achieved (40%). Since lesser degrees of obstruction tend to have hemodynamic impact only at higher degrees of coronary blood flow,[4] maximal exercise would be more likely to result in regional hypoperfusion than submaximal exercise. Finally, patients with 21 to 40% maximal coronary stenosis had a significantly higher incidence of Tl-201 defects (59% vs 27%) than patients with 20% maximal stenosis, almost all of whom had entirely normal coronary angiograms. It may therefore be inappropriate to describe exercise Tl-201 defects associated with 21 to 40% coronary lesions as "false positive."

Propranolol use: Two effects of propranolol were observed. First, since the regression coefficient for the interaction of propranolol and percent maximal stenosis was negative, the use of propranolol reduced the likelihood of a positive Tl-201 test for a given maximal coronary artery stenosis. This may reflect the fact that propranolol reduces myocardial work and, hence, cor-

onary blood flow during exercise. As discussed, lesser degrees of stenosis have hemodynamic impact only at higher levels of coronary blood flow. Therefore, with propranolol treatment, borderline coronary stenoses would be less likely to cause regional reductions in coronary blood flow and, thus, less likely to cause a Tl-201 perfusion defect.

Second, propranolol use appeared to have a positive influence on the development of a positive Tl-201 test independent of its interaction with percent maximal stenosis. This influence may be either a direct effect of propranolol on regional myocardial blood flow or Tl-201 uptake or may reflect an indirect effect of patient selection and physician prescription practices. Recent evidence suggests that patients with chest pain and normal coronary arteries angiographically may not have an entirely normal cardiovascular system.[12] Thus, patients with true myocardial ischemia may be more likely to receive propranolol from their physicians, and propranolol use may simply be a marker of underlying cardiac pathology rather than a primary causative agent in producing abnormal Tl-201 tests. Nevertheless, β_2 receptors mediating vasodilation have been described in coronary arteries,[13–15] and propranolol, which has β_1 and β_2 antagonist properties, has been demonstrated to block such adrenergic-induced coronary vasodilation.[13–15] Thus, propranolol may increase coronary vascular tone, and it is possible that Tl-201 defects associated with propranolol are related to hypoperfusion caused by β-antagonist-induced coronary vasospasm. However, regional hypoperfusion associated with segmental defects would be unexpected since differential effects of β blockade on different coronary arteries has not been described.

While propranolol has an independent positive effect and through its interaction with percent maximal stenosis a negative effect on the likelihood of a positive stress Tl-201 test result, the relative values of coefficients (Table II) shows that the net effect of propranolol is to increase the probability of a positive test response.

Exercise-induced chest pain: Chest pain elicited during the stress test was a significant predictor of a positive Tl-201 test result. Such chest pain may well be a clinical manifestation of true myocardial ischemia, because Tl-201 defects were far more common when typical angina pectoris was elicited than when atypical chest pain developed.

Patients: Earlier reports of specificity for stress Tl-201 testing have been approximately 90% for both upright[1] and supine[16] exercise. We do not know why our specificity was considerably lower (73% for 0 to 20% stenosis). It may be due to the high incidence of propranolol use in our series (45%) which the present study has shown to be a positive influence on the development of an abnormal Tl-201 stress test. In addition, all patients in the present series were symptomatic, having presented with chest pain severe enough to warrant coronary angiography, and therefore may not reflect a truly "normal" population. Nevertheless, the patient population in this study is representative of a subgroup of patients likely to undergo exercise Tl-201 testing for evaluation of chest pain.

Clinical implications: The high incidence of Tl-201 defects associated with 21 to 40% stenosis indicates that such lesions may have true hemodynamic impact. This consideration may be important in evaluating the angiographic coronary anatomy of patients who present with exertional chest pain. In addition, this relation should be considered when defining a "normal" coronary artery population for other studies. Although propranolol does not appear to affect overall sensitivity for coronary artery disease,[17] the observation that propranolol was associated with a high incidence of positive Tl-201 test responses in the presence of minor angiographic coronary disease suggests that where clinically acceptable, an attempt should be made to wean patients off β blockade before the exercise Tl-201 study.

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Collateral Circulation in Coronary Artery Disease

MacARTHUR A. ELAYDA, MD, VIRENDRA S. MATHUR, MD, ROBERT J. HALL, MD, G. ALI MASSUMI, MD, EFRAIN GARCIA, MD, and CARLOS M. de CASTRO, MD

The coronary arteriograms and left ventriculograms of 202 consecutive patients were reviewed. All had at least 75% diameter reduction of 1 or more major coronary arteries. In 127 patients (63%), at least 1 major branch was totally occluded. Collateral circulation was seen in 125 of these 127 patients (190 of 192 totally occluded arteries). Of the 75 patients without total occlusion, only 2 with 99% (or near-total) occlusion had demonstrable collateral circulation (2 of 208 arteries). In no patient with 75 to 98% diameter narrowing was collateral circulation demonstrated (0 of 164 arteries). An analysis was made of the relation between left ventricular (LV) segmental wall motion and the quality of collateral circulation in 190 totally occluded arteries among 125 patients. Of 126 arteries with good collateral circulation, LV contraction was normal in 21%, hypokinetic in 48% and akinetic/dyskinetic in 29%. Of 64 arteries with poor collateral circulation, LV contraction was normal in 23%, hypokinetic in 55% and akinetic/dyskinetic in 20%. There was no statistically significant difference between the effect of good or poor collateral circulation on LV function. These data indicate that collateral circulation cannot be seen angiographically unless there is total or near-total occlusion, and that the presence of collateral circulation does not correlate with LV wall motion abnormalties, i.e., akinetic area, despite good collateral flow or normal wall motion despite absent or poor collateral flow.

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It is generally accepted that collateral blood vessels are real and potential channels in the normal heart.[1] Collateral vessels represent alternative routes of flow that develop and enlarge as a result of a pressure difference across segments of coronary arteries caused by an obstruction.[2-8] As a result, collateral circulation is not due to formation of new vessels, but rather the utilization of vessels that preexist but are nonfunctional until the need arises.[9-12] Considerable controversy continues over the function and effectiveness of coronary vessels that act as a compensatory mechanism to protect the myocardium against ischemia. The present study was designed to study the circumstances that promote collateral circulation and their protective role. The study was prompted by the frequently asked question posed by many clinicians, "Does this patient have collaterals?" and a frequent misstatement, "This patient has good collaterals and *natural bypasses.*"

From the Division of Cardiology, the Texas Heart Institute of St. Luke's Episcopal and Texas Children's Hospitals and the Clayton Foundation for Research, Cardiovascular Laboratory, Houston, Texas. Manuscript received January 27, 1984; revised manuscript received September 10, 1984, accepted September 11, 1984.

Address for reprints: Office of the Medical Director, Texas Heart Institute, P.O. Box 20269, Houston, Texas 77225.

Methods

A total of 211 consecutive coronary angiograms and left ventriculograms of patients with significant coronary artery disease (CAD) were studied. Significant CAD was defined as at least 75% diameter reduction of 1 or more major coronary arteries. Of these 211 angiograms, 202 were selected for the study based on good quality. Selective coronary angiography was performed in multiple projections at 60 frames/s. Evaluation of the angiograms was done by at least 2 investigators, independently, and then jointly to ensure accuracy.

Stenosis of the coronary arteries was estimated as a percentage of luminal narrowing based on diameter reduction. Estimation of coronary stenosis up to 75% was done using a caliper; however, higher grades of obstruction (between 75 and 99%) were somewhat arbitrary and derived from close inspection of the involved segment through multiple views.

Collateral circulation was considered present if there was opacity of the right or its branches after injection of contrast medium into the left coronary artery, or vice versa. Collateral vessels were also considered present if the distal segment of a totally occluded vessel was opacified late after injection in the proximal segment. The actual collateral channels joining the distal and proximal segments of obstructed vessels were not necessarily visualized in each patient. The degree of opacity of the distal segment was considered an indication of the adequacy of the collateral circulation. Collaterals were considered good if the opacity of the distal segment was 50%

TABLE I Occurrence of Collateral Circulation in the Presence of 75% to 100% Stenotic Lesions

Degree of Narrowing (%)	No. of Pts	Collateral Circulation	
		With	Without
Right Coronary Artery			
75–89	20	0	20
90–98	28	0	28
99	6	1	5
100	74	74	0
Left Anterior Descending Artery			
75–89	20	0	20
90–98	38	0	20
99	23	1	22
100	73	72	1
Left Circumflex Artery			
75–89	26	0	26
90–98	30	0	30
99	17	0	17

TABLE II Distribution of Total Coronary Obstruction and Quality of Collateral Circulation

Obstructed Artery	n	Collateral Circulation		
		None	Poor	Good
Right	74	0	29	45
LAD	73	1	18	54
LC	45	1	22	22

LAD = left anterior descending artery; LC = left circumflex artery.

or more of the proximal segment, and poor if the opacity of the distal segment was less than 50% of the proximal segment.

Regional ventricular wall motion: Performance of the various left ventricular (LV) regions or segments was evaluated by biplane left ventriculography. Each region was graded as normal, hypokinetic, akinetic or dyskinetic. The relation of collateral vessels and regional wall motion was studied in all patients with complete occlusion and correlated with the adequacy of collateral circulation.

Results

In the total population, there were 127 (63%) patients in whom at least 1 major branch was totally occluded. Collateral circulation was seen in 125 of these 127 patients (190 of 192 totally occluded arteries in 127 patients). In the 75 patients without total occlusion, only 2 (3%) with 99% (or near-total) occlusion had demonstrable collateral circulation (2 of 208 arteries with 75 to 99% stenosis). The distribution of narrowings in each major artery or its branches, according to severity, and the presence of collateral vessels is listed in Table I. In the arteries critically stenosed, 75 to 99%, but not totally occluded, collateral circulation could be angiographically visualized in only 2 patients, both of whom had near-total occlusion (99% stenosis). All patients with total occlusion had demonstrable collateral circulation, with the exception of 2 in whom the occluded segments were in a totally akinetic/dyskinetic LV area. In no instance of 75 to 98% stenosis was collateral circulation demonstrated angiographically.

The quality of collateral circulation in relation to totally occluded vessels, respectively, is shown in Table II. The relation of LV segmental wall motion with the quality of collateral circulation is shown in Figure 1. No statistically significant difference was noted between the effects of poor and good collateral circulation on LV wall motion (chi-square analysis).

Discussion

Our results differ from previous observations by other investigators who claim observance of collateral circulation in vessels with stenoses of 50 to 95%.[6,7,13–19] These claims have led clinicians to ask the question, "Does my patient have collaterals?", implying that some patients with 50 to 95% stenosis have collaterals and others do not and patients with collaterals have a better prognosis. Although lesions with 50 to 90% occlusion *can* produce myocardial ischemia and anginal pain, according to our data they are never accompanied by collateral circulation that is visible angiographically. Our data indicate that angiographically demonstrable collaterals depend on the presence of a totally occluded artery rather than any variability from patient to patient; as collateral vessels are almost always present if an artery is totally occluded. It appears from our data that the resting pressure in the distal segment of a stenosed artery must be very different in patients with or without 100% obstruction. In the presence of 100% obstruction, the distal pressure is low enough to permit angiographic collateral flow; with less than 100% obstruction, the distal pressure may be quite low but still not as low as in 100% occluded arteries and therefore angiographic collateral flow does not occur. An older report that claimed presence of

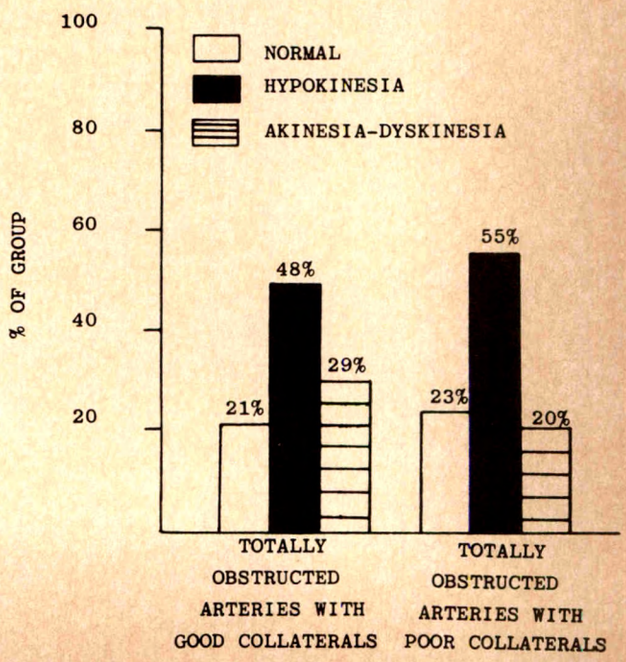

FIGURE 1. Left ventricular segmental wall motion in relation to the quality of collateral circulation. The proportion of normal, hypokinetic and akinetic segments is similar in the group with good and the group with poor collateral vessels.

collaterals in patients with 50 to 75% stenosis[16,19] might have observed a 50% lesion of a major vessel and missed the 100% occlusion of a branch and what was actually seen as collaterals was only for that branch.

Possible reasons for failure to demonstrate collaterals in totally occluded arteries include: (1) poor angiographic technique; (2) failure to use nitroglycerin, which has been shown to elicit primary vasodilation of coronary collateral channels[8,20]; and (3) failure to properly visualize the area of the missing vessel in the late phase. These latter techniques are now used routinely and have greatly helped in the study of difficult cases.

Controversy continues over the role of collateral circulation in preserving LV function in patients with CAD. Some investigators have reported that function may be substantially better when collateral vessels have developed[9,17,24–26]; our data and data from other studies[13–15,21–23] do not support this. Our results show that normal wall motion distal to an occluded segment is possible, even with poor collateral circulation. We have no good explanation for this, but the conclusion that infarction is avoidable even with total occlusion of an artery and poor collaterals is inescapable. Conversely, LV segmental motion can be akinetic despite good collateral circulation. We can neither retrospectively determine if the collateral circulation was good at the time of infarction nor determine the temporal sequence of total occlusion, good collateral development and clinical infarction. We must draw 1 of 2 conclusions: (1) infarction took place despite good collateral vessels, or (2) good collaterals developed after infarction in an akinetic or dyskinetic area.

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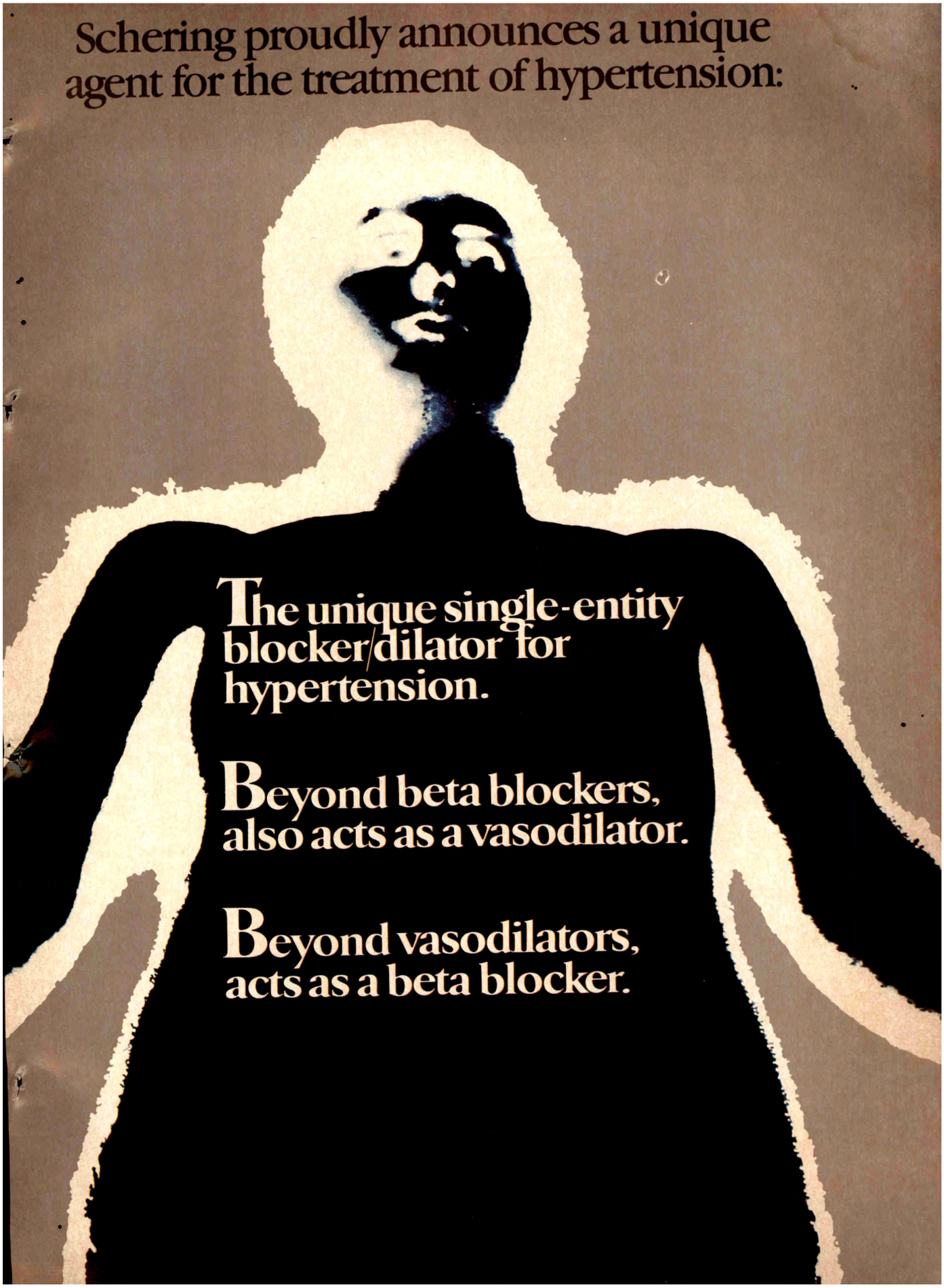

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...brief summary of prescribing information

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BRIEF SUMMARY

INDICATIONS AND USAGE
NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS
NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia. (See WARNINGS.)

WARNINGS
Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hypoglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS
General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately, should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effect was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	1	0	2	0
taste distortion	<1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl

Daily Dose (mg)	200	300	400	600	800	900	1200	1600	2400
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10

Labetalol HCl (continued)

Daily Dose (mg)	200	300	400	600	800	900	1200	1600
Number of Patients	522	181	606	608	503	117	411	242
Nausea	<1	0	1	2	4	0	7	11
Vomiting	0	0	<1	<1	<1	0	1	2
Dyspepsia	1	0	2	1	1	0	2	2
Paresthesias	2	0	2	2	1	1	2	5
Nasal Stuffiness	1	1	2	2	2	2	4	5
Ejaculation Failure	0	2	1	2	3	0	4	3
Impotence	1	1	1	1	2	4	3	4
Edema	1	0	1	1	1	0	1	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive anti-nuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See **CONTRAINDICATIONS.**

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE
Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a beta$_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION
DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered tid may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg bid.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED
NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

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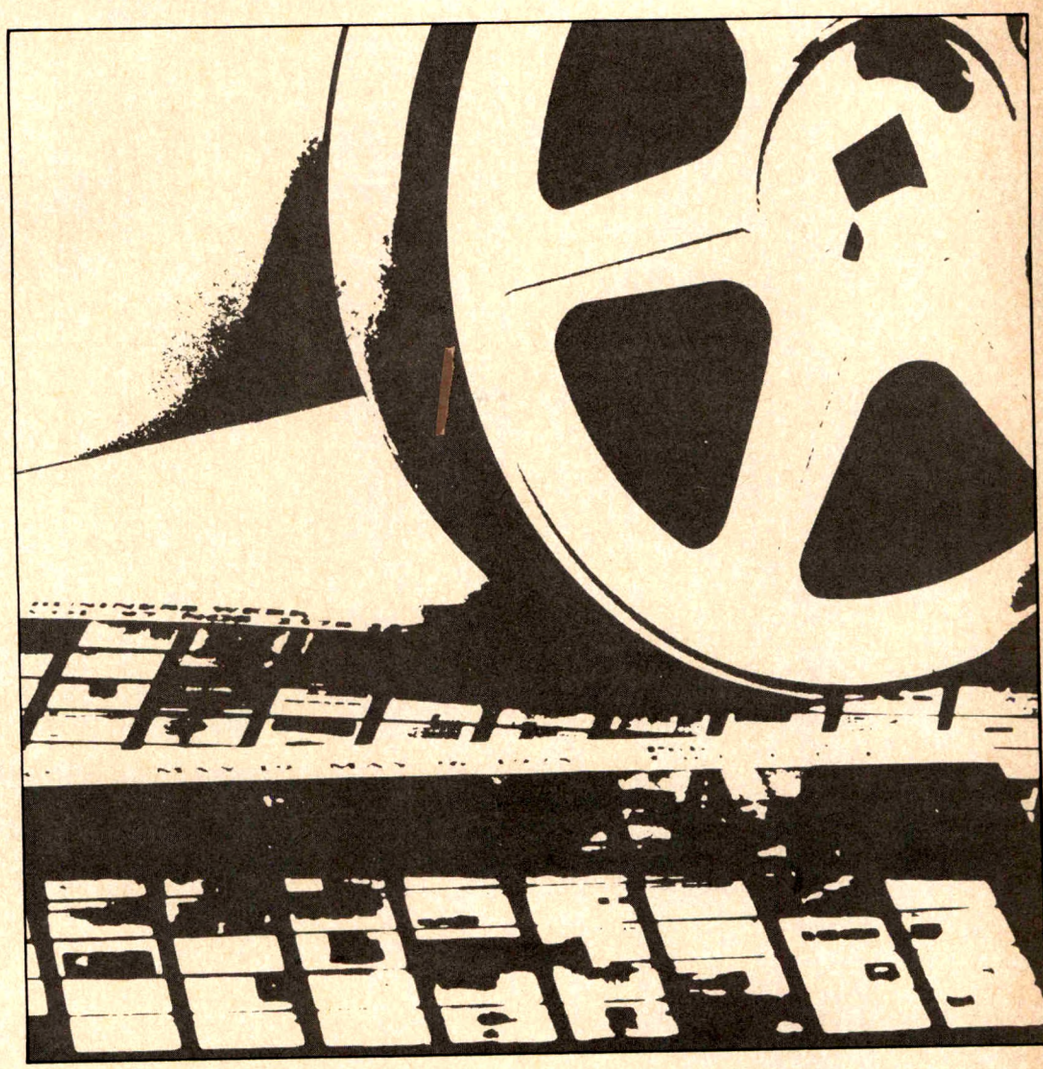

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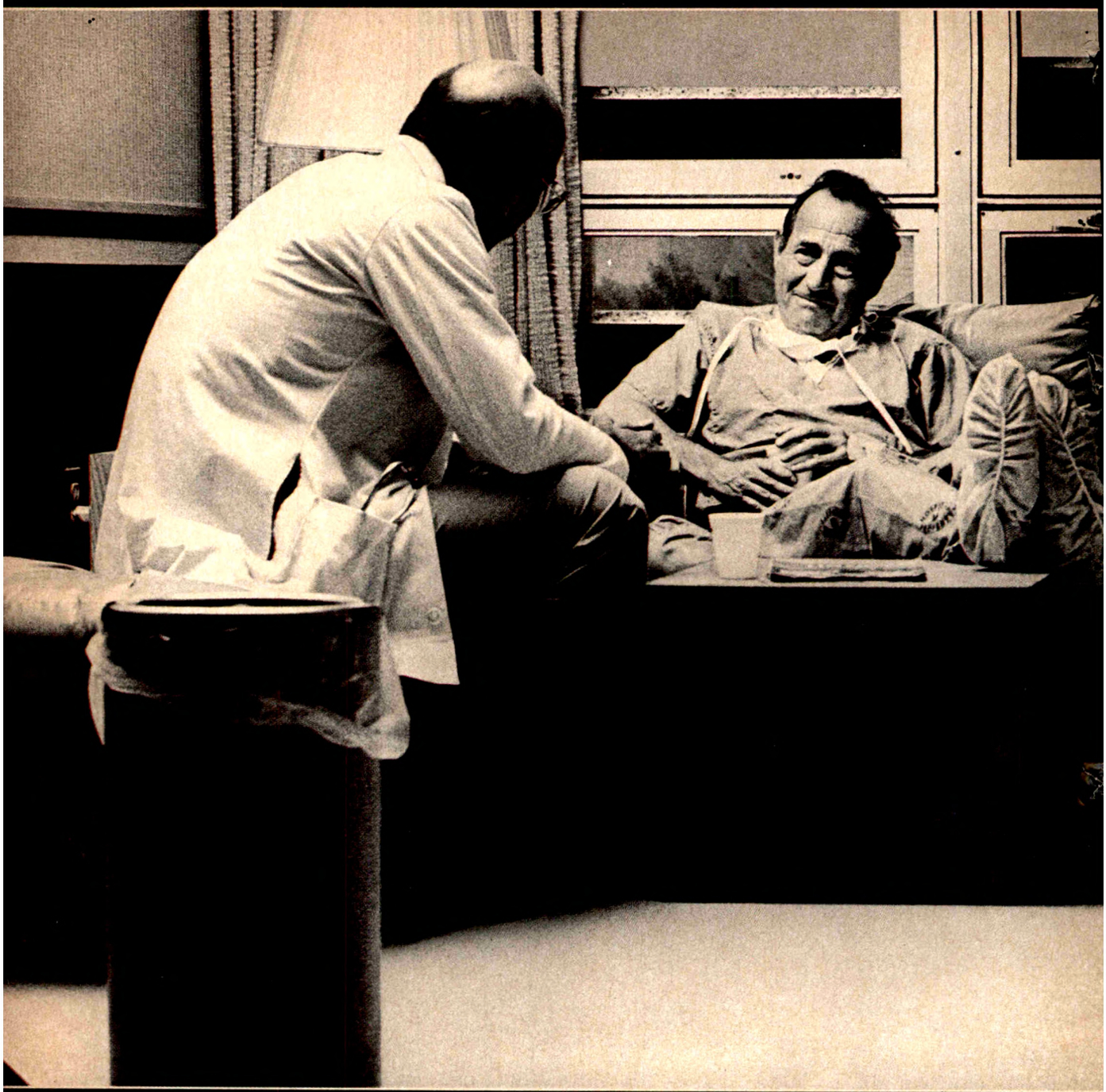

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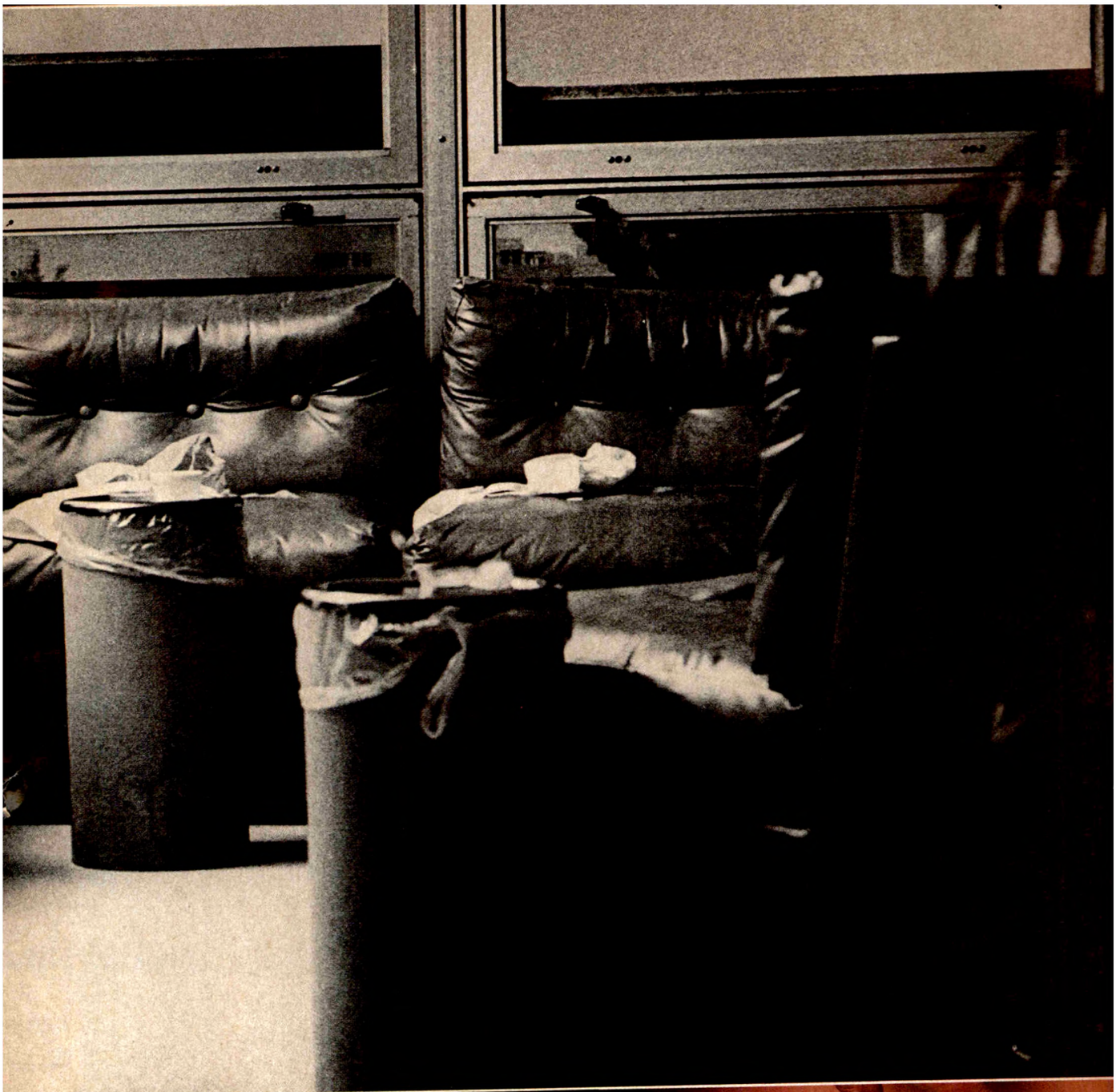

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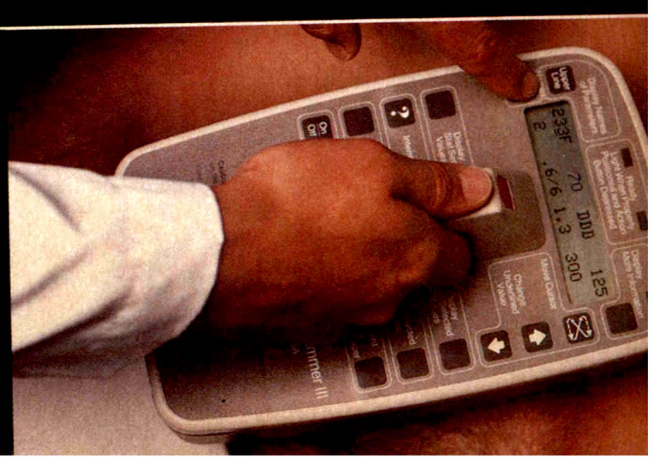

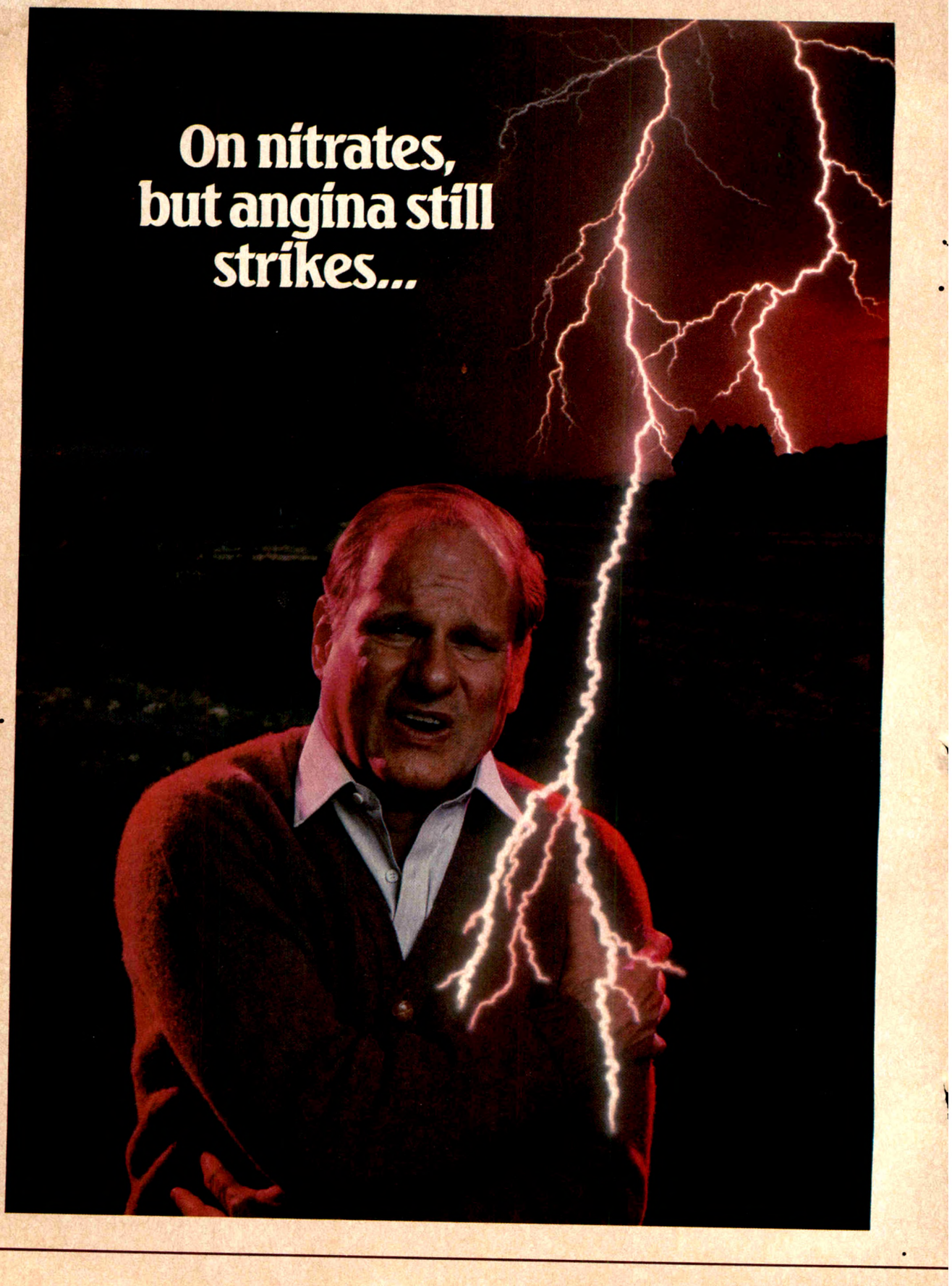
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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets. July 1982

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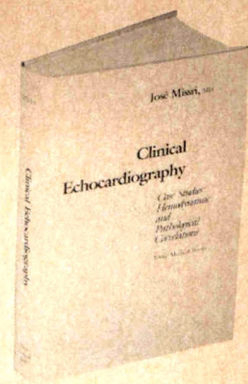

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by José Missri, MD
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Influence of Magnesium Ion on Human Ventricular Defibrillation After Aortocoronary Bypass Surgery

BERNICE R. HECKER, MD, CAROL L. LAKE, MD, IRVING L. KRON, MD, ROBERT M. MENTZER, MD, IVAN K. CROSBY, MD, STANTON P. NOLAN, MD, and RICHARD S. CRAMPTON, MD

The administration of magnesium ion (Mg^{++}) has been reported to defibrillate the ventricles and to decrease the incidence of arrhythmias after cardiopulmonary bypass. In a prospective study of 76 randomly selected patients undergoing coronary artery bypass grafting, patients received either no Mg^{++}, 0.25 mEq/kg of Mg^{++} during cardiopulmonary bypass with the aorta clamped, or 0.375 mEq/kg of Mg^{++} before cardiopulmonary bypass. Spontaneous resumption of a cardiac rhythm or spontaneous defibrillation during reperfusion was not significantly affected by Mg^{++} administration. However, the number of shocks to initial and to sustained defibrillation and the energy required for the last direct-current shock was greatest in patients who received Mg^{++} before bypass and in those whose plasma Mg^{++} was greater than 2.26 mg/dl. Thus, the administration of Mg^{++} may have adverse effects on the heart if intraoperative plasma Mg^{++} exceeds 2.26 mg/dl.

(Am J Cardiol 1985;55:61–64)

Techniques or interventions augmenting spontaneous resumption of cardiac electrical activity rather than permitting the onset or persistence of ventricular fibrillation (VF) during reperfusion are desirable for preventing myocardial injury from the energy or current of direct-current shocks.[1,2]

Magnesium ion (Mg^{++}), which is often abnormally low in patients preoperatively or during cardiopulmonary bypass,[3–6] stabilizes membrane conductance preserving ionic gradients, maintains a steady resting potential and normalizes cellular electrical responses.[7–9] During cardiac surgery,[3,9,13] cardiac arrhythmias[7,10] or acute myocardial infarction,[11,12] an increase in the frequency of spontaneous defibrillation[13] and a decrease in the occurrence of arrhythmias have been noted after the administration of Mg^{++} salts.[7–12] We related the effects of administration of Mg^{++} to spontaneous cardiac electrical activity at the time of reperfusion, to energy, current, resistance of shocks to defibrillate and to the number of shocks required to defibrillate patients undergoing coronary bypass grafting.

From the Departments of Anesthesiology, Surgery (Thoracic and Cardiovascular), and Internal Medicine (Cardiology), University of Virginia Medical Center, Charlottesville, Virginia. This study was supported by the American Heart Association, Virginia Affiliate, Richmond, Virginia. Manuscript received June 1, 1984; revised manuscript received August 29, 1984, accepted August 31, 1984.

Address for reprints: Carol L. Lake, MD, Department of Anesthesiology, Box 238, University of Virginia Medical Center, Charlottesville, Virginia 22908.

Methods

This study was performed between July 1982 and June 1983 on a randomly selected population of 76 patients who underwent coronary artery bypass grafting and who did not have a history of arrhythmias or a need for antiarrhythmic drugs. No patient had congestive heart failure or an ejection fraction less than 0.5.

Anesthetic and surgical techniques were consistent throughout the period of study. Before the induction of anesthesia, a blood sample was obtained for determination of plasma Mg^{++}. Normal values were 1.8 to 2.8 mg/dl. The patient population was prospectively classified into 3 groups. Group I received no supplemental Mg^{++}; group II received Mg^{++}, 0.25 mEq/kg body weight as sulfate, intravenously during cardiopulmonary bypass with the aorta clamped; group III received Mg^{++}, 0.375 mEq/kg as sulfate, intravenously before cardiopulmonary bypass. At the time of reperfusion, 3 types of electrical events occurred: reperfusion electrical activity, defined as any nonfibrillatory rhythm including ventricular asystole; spontaneous defibrillation defined as VF that terminated spontaneously; and primary VF, defined as VF that requried direct-current shock. At the time of spontaneous electrical activity or defibrillation or before and after direct-current shocks, the following variables were measured: (1) plasma Mg^{++} levels, using atomic absorption spectrophotometry; (2) plasma ionized calcium levels, using the Orion SS20 analyzer; (3) plasma potassium levels, using a Nova Biomedical direct potentiometer; (4) arterial P_{O_2}, P_{CO_2} and pH, using standard electrodes and corrected to the patient's perfusion temperature; (5) plasma norepinephrine and epinephrine levels, using high-performance liquid chromatography; (6) mean systemic, pulmonary and coronary perfusion

TABLE I Differences Among Groups Receiving Magnesium*

Variable (Mean ± SD)	Group I Control (n = 24)	Group II Mg^{++} During Bypass (n = 24)	Group III Mg^{++} Before Bypass (n = 24)
Plasma Mg^{++} (mg/dl)	1.4 ± 0.2†,§	2.5 ± 0.3‡	2.3 ± 0.3‡
Time after Mg^{++} Admin. (min)	0 ± 0†,§	47 ± 12‡,§	92 ± 36†,‡
Perfusion temperature (deg C)	38.8 ± 0.8†,§	36.8 ± 3.7‡	38.2 ± 1.0†,‡
Ventricular thickness (cm)	0.9 ± 0.2†	0.8 ± 0.2‡,§	1.0 ± 0.2†

* Data from 4 patients excluded because of excessive cardioplegia or enlarged heart.

† $p < 0.05$ compared with values in group II; ‡ $p < 0.05$ compared with values in group I; § $p < 0.05$ compared with values in group III.

Admin. = administration; deg C = degrees centigrade; Mg^{++} = magnesium ion; SD = standard deviation.

pressures, using Bentley Trantec transducers and Hewlett-Packard pressure modules with systemic vascular resistance calculated using the standard formula; (7) myocardial temperature, using a Wilton Webster (NTM-100) probe; (8) perfusion temperature, using an in-line thermistor. The duration of cardiopulmonary bypass, myocardial ischemia, reperfusion, and time from Mg^{++} administration to event were noted. One patient who received Mg^{++} less than 15 minutes before aortic unclamping was excluded.

Direct-current shocks were administered using a Physio Control Series 640 defibrillator, delivering between 0 and 320 J. An initial shock of 1 J was given. If needed, a second shock at 2.5 J was given. Thereafter, energy was increased by 2.5-J increments until defibrillation. If a shock succeeded, but the heart refibrillated, the next shock was given at the last successful energy. Current was measured with a Tektronix P6303 current probe and amplifier. Resistance was determined from calibration curves of energy and current created by discharging the defibrillator into known loads.

Instillation of high-potassium cardioplegia was performed whenever myocardial septal temperature was above 18°C or cardiac electromechanical activity was noted. Cardioplegic solution consisted of potassium chloride, 26 mEq, 50% dextrose, 27 ml, sodium hydroxide, 1N, 0.15 ml in 1 liter of lactated Ringer's solution cooled to 4°C. When only myocardial cooling was necessary, Polyonic®, an electrolyte solution that contains potassium, 4 mEq/liter, and magnesium, 3 mEq/liter, was instilled. The adequacy of myocardial preservation was assessed by noting the type and volume of cardioplegic solution administered, use of topical hypothermia and duration of myocardial temperature less than 18°C. Two patients who received more than 1,900 ml of cardioplegic solution were excluded from group III.

At cardiac catheterization, biplane cineangiograms were recorded on 35-mm film in the right and left anterior oblique positions. The area-length method was used to calculate end-diastolic volume. Wall thickness was measured halfway between the equator and the base of the heart at end-diastole. Mass was then calculated using the method of Rackley et al[14] and Wynne et al.[15] Two patients with estimated heart weights of more than 300 g, 1 from group III and 1 from group I, were excluded.

All data are expressed as mean ± standard deviation and were stored on a PDP 1144 computer. Statistical analyses were performed by the Statistical Analysis System (SAS Circle) using general linear modeling, Duncan's multiple-range, chi-square, Fisher's 1- and 2-tailed tests, or Student *t* test.

TABLE II Overall Outcome Characteristics

Cardiac Activity (Unclamping)	Group I (n = 24) Control	Group II (n = 24) Mg^{++} During Bypass	Group III (n = 24) Mg^{++} Before Bypass
Reperfusion electrical activity	19	22	18
Developed fibrillation during reperfusion	13	19	14
Spontaneous defibrillation	2	0	0
Direct-current shocks	3	2	6

Mg^{++} = magnesium ion.

Comparisons of spontaneous electrical events after reperfusion, success or failure of direct-current shock, and energy, current and resistance of defibrillation, were made among and across groups. Data were analyzed across groups for selected plasma Mg^{++} and selected plasma Mg^{++} associated with time of administration (i.e., before or during bypass). Plasma Mg^{++} levels above and below 2.26 mg/dl were arbitrarily chosen to provide sufficient number of patients for statistical analyses at higher and lower Mg^{++} levels. This resulted in separation of the patient population into 5 groups. Patients in group A received no Mg^{++}. Patients in group B received Mg^{++} during bypass and had Mg^{++} levels that exceeded 2.26 mg/dl. Patients in group C received Mg^{++} during bypass levels of less than 2.26 mg/dl. Patients in group D received Mg^{++} before bypass and had Mg^{++} levels of greater than 2.26 mg/dl. Patients in group E received Mg^{++} before bypass, but had Mg^{++} levels of less than 2.26 mg/dl. In summary, 4 patients were eliminated from the study for excessive cardioplegic volume (n = 2) and enlarged heart (n = 2).

Results

The mean control Mg^{++} level was 2.02 ± 0.19 mg/dl (range 1.45 to 2.48) in the 72 patients in the study before the induction of anesthesia. Four patients in group I, 1 in group II and 2 in group III had hypomagnesemia (<1.8 mg/dl). The plasma Mg^{++} concentration decreased to 1.4 ± 0.2 mg/dl ($p = 0.0001$) in control patients who did not receive intraoperative Mg^{++}, whereas it increased significantly in patients in group II (2.5 ± 0.3 mg/dl, $p = 0.0001$) and group III (2.3 ± 0.3 mg/dl, $p = 0.0001$) (Table I). Significant differences were found in 3 other variables (Table I). The time from onset of administration of Mg^{++} to the sampling for the study was longest in group III. The perfusion temperature was higher in groups I and III than in group II. Left ventricular thickness was greatest in group III (Table I). Patients in groups II and III received slightly more cardioplegia containing Mg^{++} than those in group I, although the difference was not statistically significant.

The prevalence of VF on reperfusion and the occurrence and type of other dysrhythmias were similar in all 3 groups (Table II). Spontaneous defibrillation occurred in 2 control patients (group I) and in none of the patients treated with Mg^{++}, as the initial reperfusion event. However, the incidence of reperfusion VF was highest in group III (35%) and lowest in group II (18%) (Table II). No significant differences in the incidence of spontaneous resumption of electrical activity or energy and current required to defibrillate were seen as

a result of Mg^{++} administration alone. However, group III patients required more shocks to the first defibrillation (3.1 ± 1.8 vs 2.2 ± 1.0) than group II patients. Although not significant, group III patients also required the greatest number of shocks to sustained defibrillation. Development of VF after initial spontaneous electrical activity occurred frequently in all patients, although group I, which included patients who received no supplemental Mg^{++}, had the lowest incidence of fibrillation—68%, compared with 86% in group II and 78% in group III. Atrial or ventricular arrhythmias after discontinuation of bypass were seen more often in group III than in group I. Other events after bypass or after operation, such as death, ventricular failure, or need for antiarrhythmic, inotropic or vasodilator drugs, occurred so infrequently as to preclude valid statistical analysis.

The relation of plasma Mg^{++} concentration and time of administration of Mg^{++} to spontaneous electrical activity after aortic unclamping, number of direct-current shocks and levels of energy, current and resistance were also investigated. When plasma Mg^{++} was greater than 2.26 mg/dl (group D), higher levels of energy were needed to defibrillate (Table III). The number of shocks necessary for initial and sustained defibrillation in patients with a serum Mg^{++} level of more than 2.26 mg/dl who received Mg^{++} before bypass (group D) was greater than that in any other groups (Table III). The energy required for sustained defibrillation tended to be greater in this group (Table III).

TABLE III Effect of Magnesium Concentration

	Group A		Group B		Group C		Group D		Group E	
	No Mg^{++} (Total n = 24)		Mg^{++} >2.26 mg/dl (Total = 17)		Mg^{++} ≤2.26 mg/dl (Total n = 7)		Mg^{++} Before Bypass & Mg^{++} >2.26 mg/dl (Total n = 15)		Mg^{++} Before Bypass & Mg^{++} ≤2.26 mg/dl (Total n = 9)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Incidence of spontaneous events	21		15		7		9		9	
Spontaneous electrical activity	3		2		0		6		0	
Direct-current shock										
Direct-current shock	5		4		1		2		1	
Successful first shock (no. of pts.)										
No. of shocks	16	3 ± 2	14	2 ± 1	4	2 ± 1	12	5 ± 2	8	2 ± 1
First successful shock	16	3 ± 2	14	4 ± 2*	4	2 ± 1	12	5 ± 2†	8	3 ± 1
Last successful shock (sustained defib)										
Last successful shock	16	6.5 ± 3.9	14	5.3 ± 3.2	4	3.8 ± 1.4	12	9.6 ± 12.9	8	3.6 ± 2.1
Energy (J)	10	8.8 ± 2.9	8	8.4 ± 2.7	3	7.3 ± 1.6	10	9.1 ± 2.0	8	6.9 ± 2.4
Current (A)										
Cumulative energy (J)	16	10.3 ± 9.5	14	7.0 ± 6.0	4	3.9 ± 0.8	12	22.9 ± 41.2	8	6.0 ± 4.8
First successful shock	16	12.4 ± 12.7	14	14.4 ± 14.4	7	8.7 ± 8.0	12	29.0 ± 41.4	8	6.6 ± 5.5
Last successful shock										
Cumulative current (A)										
First successful shock	10	18.1 ± 12.2	7	15.2 ± 9.6	3	9.8 ± 0.5	9	21.8 ± 14.9	8	13.6 ± 8.5
Last successful shock	10	22.1 ± 15.1	7	25.9 ± 14.8	3	13.1 ± 5.0	8	28.1 ± 17.5	8	14.7 ± 9.7

* p = 0.05 vs group C by 1-way analysis of variance; † p = 0.05 vs groups A, C and E. Abbreviations as in Table I.

Discussion

Magnesium ion influences cardiac automaticity, excitability, VF threshold, conduction and contractility. Ventricular tachycardia and VF, coronary spasm and supraventricular arrhythmias occur with hypomagnesemia,[12] particularly with digitalis toxicity.[7–12] Magnesium treatment is effective even in hypokalemia.[7] Patients who undergo open-heart surgery with cardiopulmonary bypass have low serum Mg^{++} levels during the perioperative period.[3–5] Büky[13] gave intravenous Mg^{++}, 0.1 mg/kg, during reperfusion. Spontaneous defibrillation was noted within minutes in 18 of 27 patients and facilitation of defibrillation was noted in the remaining patients. Krasner et al[9] documented a decrease in the QTc interval in patients who received sufficient oral magnesium preoperatively to normalize serum Mg^{++} levels. Such a decrease in the QTc interval would be expected to reduce vulnerability to ventricular arrhythmias if this interval had been lengthened by an arrhythmogenic mechanism such as hypomagnesemia or hypokalemia. Intravenous Mg^{++} terminated torsades de pointes in normal patients with prolonged QTc intervals.[16]

When Mg^{++} was infused as a component of cardioplegic solutions, a decrease in arrhythmias and an increase in cardiac contractility occurred after reperfusion.[17–19] However, some investigators found undesirable effects of intracoronary administration of Mg^{++}.[18–20] When cardioplegic solutions contained more than 15 m*M*/liter (360 mg/liter) of Mg^{++}, Hearse et al[18] observed lower aortic pressure, flow and heart rate on reperfusion of isolated rat hearts. When Shapira et al[20]

compared patients with potassium or blood cardioplegia with those receiving Mg^{++} cardioplegia, they found depression of maximal contractile element velocity and increased left ventricular end-diastolic pressure in the group treated with Mg^{++}. No differences in the incidence of postoperative cardiac failure could be attributed to the Mg^{++} content or volume of cardioplegia solution administered to our patients.

In our study, significant differences appeared in plasma Mg^{++}, time from administration of Mg^{++} to cardiac event, perfusion temperature and left ventricular thickness. Neither of the latter 2 variables is known to affect spontaneous defibrillation, requirements for levels of energy or current, or success of direct-current shocks.[21] Our results then, may be attributed to the serum Mg^{++} level or the duration of myocardial exposure to Mg^{++}.

Although our observations differ from those in several reports,[10–13] they are not unexpected. Calcium entry into myocardial cells is competitively antagonized by Mg^{++},[8] yet electrical stability depends on adequate extracellular concentrations of both calcium and Mg^{++}.[24] Slow channel sodium influx and cardiac automaticity, cardiac excitability, the velocity of atrial and ventricular conduction, and the development of ventricular tension—all processes dependent on the flow of calcium ion into myocardial cells—are depressed by administration of Mg^{++}.[7,10,22,23] The reduction in spontaneous resumption of cardiac rhythm seen in our patients and in those of Shapira et al[20] may be due to a relative excess of Mg^{++} hyperpolarizing the cell membrane. Hyperpolarization of the myocardial cell by elevation of extracellular Mg^{++} would necessitate greater current to depolarize the cell membrane and account for the depression of reperfusion electrical activity. On the other hand, reduction of extracellular Mg^{++} partially depolarizes the cell and causes arrhythmias.[25] By decreasing potassium conductance, Mg^{++} maintains a more negative potential across the cell membrane.[7,8,10,12]

Variation of our findings from those of previous investigators needs explanation. First, Büky's[13] study was performed using ischemic arrest rather than cardioplegia and topical hypothermia for myocardial preservation. Second, the effects of Mg^{++} on ischemic fibrillating hearts[26] may well differ from hearts subjected to current myocardial preservation techniques.[18] Third, we correlated our results with the serum Mg^{++} attained rather than with the dose of Mg^{++} administered alone. Serum Mg^{++} levels observed in our patients may correspond to higher extracellular Mg^{++} levels than those reached in other studies. Also, serum Mg^{++} in our patients was more acutely achieved, allowing little time for equilibration compared with oral administration. Fourth, although this was an unblinded study, criteria for patient inclusion, anesthetic and intraoperative management, and surgical technique were unchanged during the 12 months of study, so that differences among groups, except by chance, seemed unlikely. Finally, because earlier investigators did not eliminate or control other variables affecting myocardial activity and defibrillation, such as myocardial temperature or serum potassium concentration,[21] their results differed from ours.

Conclusion: We found that administration of intravenous Mg^{++} to attain normal plasma levels did not facilitate ventricular defibrillation. Moreover, if Mg^{++} is given before cardiopulmonary bypass, more direct-current shocks of higher energy levels are needed to defibrillate. With current myocardial preservation techniques, the prophylactic administration of intravenous Mg^{++} before cardiopulmonary bypass may have adverse effects on the heart when attained plasma levels exceed the midnormal range.

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Remnant Saphenous Veins After Aortocoronary Bypass Grafting: Analysis of 3,394 Centimeters of Unused Vein from 402 Patients

BRUCE F. WALLER, MD, and WILLIAM C. ROBERTS, MD

To assess the status of a saphenous vein (SV) excised for coronary artery bypass grafting (CABG), 3,394 cm of remnant SV from 402 patients who underwent CABG were examined. The SV remnants were 0.5 to 52 cm long (mean 8.4). They were sectioned into 5-mm-long segments, and the resulting 6,788 five-millimeter segments were examined histologically: 5,896 (87%) were narrowed 0 to 25% in cross-sectional area by fibrous tissue; 853 (12%) were narrowed 26 to 50%; 23 (0.6%), 51 to 75%, and 16 (0.4%) segments were narrowed 76 to 100%. Of the 16 segments severely narrowed, 7 (44%) were nearly totally occluded by fibrous tissue. In 17 patients who died within 24 hours of CABG, similar degrees of luminal narrowing were observed in remnant segments and in utilized segments of SV. Thus, significant preexisting luminal narrowing of SV used for CABG is infrequent. The intimal fibrous thickening is variable within the same vein when each 5-mm-long segment is analyzed; it is variable from 1 vein to another in the same patient, and it varies among patients.

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Many studies describing early and late morphologic changes occurring in the saphenous vein (SV) used for coronary artery bypass grafting (CABG) have been published.[1–17] Little attention has been focused, however, on the status of the excised SV not used for CABG.[18–20] This study describes morphologic findings in remnant portions of excised SV from 402 patients who underwent CABG.

Methods

Veins studied: Remnants of operatively excised SVs were examined from 402 patients who underwent CABG at the National Heart, Lung, and Blood Institute between January 1972 and December 1981. At the time of CABG, the SV to be used for bypass grafting was isolated between the ankle and knee or thigh or both areas from 1 or both legs. After attached veins were ligated, the SV was removed and washed with heparinized saline solution. All unused segments of SV were submitted for gross and histologic examination. The submitted remnant SV was not simply discarded portions of abnormal SV, but represented all unused segments of SV. The length of the unused segment was measured (in centimeters) and the entire SV remnant was sectioned into 5-mm-long segments (Fig. 1 and 2). The segments were dehydrated, embedded in paraffin, sectioned and stained by the Movat pentachrome method. The percent of cross-sectional area (XSA) luminal narrowing of each SV segment was graded histologically, after magnification to about 40 times, into 4 categories: 0 to 25, 26 to 50, 51 to 75 and 76 to 100 (Fig. 1, 3 and 4). The internal elastic membrane was considered the normal outer rim of the lumen. A total of 3,394 cm of remnant SV were examined (Table I).

Patients: The 402 patients were 34 to 75 years old (mean 56): 16 (4%) were 34 to 40; 77 (19%) were 41 to 50; 184 (46%) were 51 to 60; 115 (29%) were 61 to 70; and 10 (2%) were 71 to 80 (Table I). Of the 402 patients, 337 (84%) were men, from whom 2,789 (82%) cm of remnant SV were examined. No patient had previous CABG, a known history of phlebitis or other diseases of the leg veins, and none had preoperative venograms.

Comparison of unused segments of saphenous vein with segments used as aortocoronary bypass grafts: Of the 402 patients who underwent CABG, 17 (4%) died within 24 hours of operation, and a necropsy was performed (Table II). Of these 17 patients, 13 (76%) could not be separated from the bypass pump, 1 died 6 hours and 3 died 24 hours after operation. These 17 patients had 327 cm of aortocoronary SV bypass conduit available for comparison with 169 cm of their respective SV remnants (Table II). The 17 necropsy patients were of similar age (34 to 68 years, mean 54) and sex (12 men, 71%) to the remaining 385 living patients. The percent of 5-mm segments of SV narrowed to various degrees was similar in 654 SV segments from bypass grafts compared with 338 SV segments from submitted remnants: 0 to 25%: graft = 94%,

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received and accepted September 5, 1984.

. Address for reprints: Bruce F. Waller, MD, Department of Pathology, University Hospital, N340, Indiana University School of Medicine, Indianapolis, Indiana 46223.

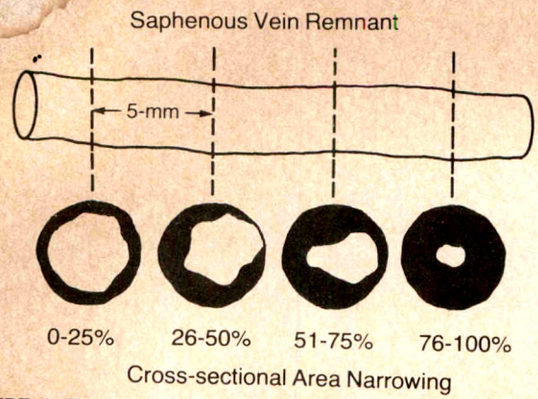

FIGURE 1. The method of sectioning of saphenous vein remnants at 5-mm intervals and the 4 grades of luminal cross-sectional area narrowing.

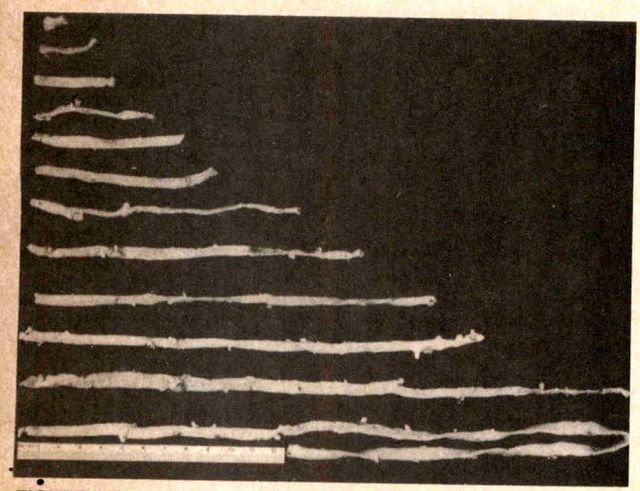

FIGURE 2. Twelve saphenous vein remnants showing the wide range in specimen lengths. The remnants in these 12 patients were 1 to 52 cm long.

remnant = 92%; 26 to 50%: graft = 6%, remnant = 8%; 51 to 100%: graft and remnant = 0 (Table II).

Histology of normal saphenous vein: The wall of the human SV contains a thin intima, separated from media by a rudimentary, fragmented internal elastic membrane. The media consists of 2 layers of smooth muscle cells: an internal longitudinal layer mixed with bundles of collagen and an external circular layer. The adventitia is composed of bundles of collagen, scattered foci of smooth muscle cells and vasa vasorum. At the insertion of venous valves, the medial longitudinal layer usually is thickened.

Results

Remnant length: The SV remnants were from 0.5 to 52 cm long (mean 8.4) (Table I, Fig. 2). The average length of unused portions of SV was similar in men (8.3 cm) and women (9.3 cm), and in younger (50 years or younger [8.8 cm]) and older (older than 50 years [8.4 cm]) patients.

Degrees of cross-sectional area luminal narrowing: SV luminal narrowing consisted of various degrees of intimal fibrous thickening composed of acellular connective tissue. The amount of luminal XSA narrowing in 6,788 five-millimeter SV segments graded histologically was: 0 to 25% XSA = 5,896 (87%) segments; 26 to 50% = 853 (12%); 51 to 75% = 23 (0.6%); and 76 to 100% = 16 (0.4%) segments (Table I, Fig. 3 to 6). Of 5,896 segments narrowed 0 to 25% in XSA by fibrous tissue, only 649 (11%) segments were narrowed to 0 to 5% (i.e., virtually normal). Of 16 segments (from 10 patients) narrowed 76 to 100% in XSA, 7 (44%) segments (from 7 patients) were narrowed 95 to 100% (i.e., virtually occluded) (Fig. 4D, 5 and 7).

Relation of amounts of saphenous vein intimal thickening to sex: The relation between various amounts of XSA narrowing and sex is summarized in Table I and Figure 8. Of 5,578 SV segments from 337 men, 13 (0.5%) segments were narrowed 76 to 100% in

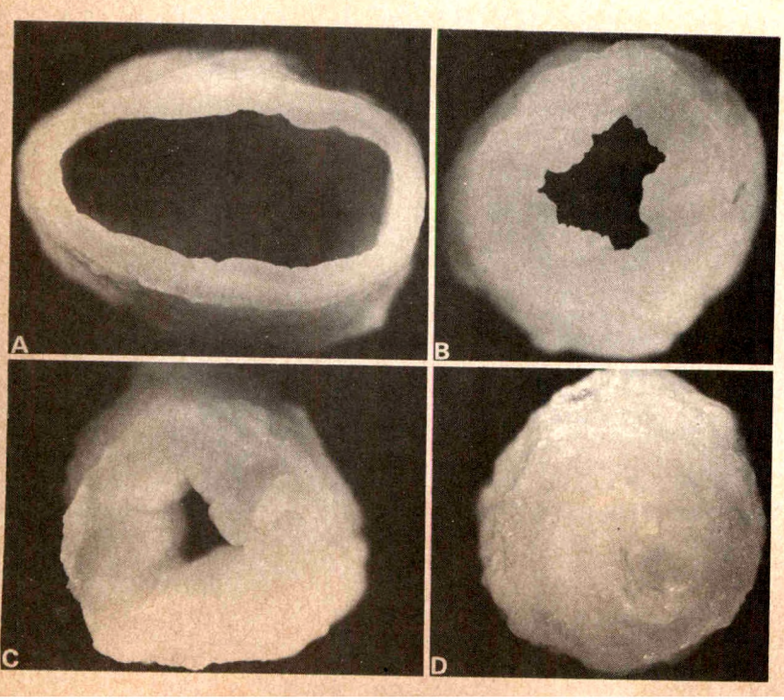

FIGURE 3. Photomacrographs of 4 saphenous vein remnants showing the 4 grades of cross-sectional area narrowing: **A,** (S80-2) 0 to 25%; **B,** (S78-103) 26 to 50%; **C,** (S77-17) 51 to 75%; **D,** (S80-92) 76 to 100%.

TABLE I Certain Clinical Findings in 402 Patients Undergoing Aortocoronary Bypass Grafting and Morphologic Observations in 3,394 CM of Remnant Saphenous Vein

Age (yr) (range, mean)	No. of Pts	Sex M:F	L of SV Remnant (cm)	Total L (cm)	Total 5-mm Seg	No. (%) Narrowed to Various Amounts in XSA by Intimal Fibrosis			
						0–25	26–50	51–75	76–100
34–40 (38)	16	15:1	4–24 (9.4)	150	300	231 (77)	65 (22)	3 (0.6)	1 (0.4)
41–50 (47)	77	69:8	0.5–35 (8.1)	620.5	1,241	1,087(87)	146(12)	1 (0.2)	7 (0.8)
51–60 (56)	184	150:34	0.5–52 (8.2)	1,500	3,000	2,640 (88)	346 (11)	10 (0.6)	4 (0.4)
61–70 (65)	115	96:19	1–34 (9.1)	1,046	2,092	1,818 (87)	264 (12)	6 (0.5)	4 (0.5)
71–80 (72)	10	7:3	3–10 (7.8)	77.5	155	120 (77)	32 (21)	3 (2)	0
Subtotal Men: 34–73 (55)		337 M (84%)	0.5–52 (8.3)	2,789	5,578	4,889 (87)	658 (12)	18 (0.5)	13 (0.5)
Women: 40–75 (58)		65 F (16%)	1–34 (9.3)	605	1,210	1,007 (83)	195 (16)	5 (0.6)	3 (0.4)
Total 34–75 (56)	402	337:65	0.5–52 (8.4)	3,394	6,788	5,896 (87)	853 (12)	23 (0.6)	16 (0.4)

L = length; Seg = segments; SV = saphenous vein; XSA = cross-sectional area.

XSA, 18 (0.5%) were narrowed 51 to 75%, and 5,547 (99%) segments were narrowed 0 to 50%. Similarly, of 1,210 SV segments from 65 women, 3 (0.4%) segments were narrowed 76 to 100% in XSA, 5 (0.6%) were narrowed 51 to 75%, and 1,202 (99%) were narrowed 0 to 50% (Fig. 8). Significant differences in amounts of XSA narrowing between men and women occurred only in the 0 to 50% category. Compared with men, women had a significantly greater percent of SV narrowed 26 to 50% in XSA (16 vs 12%), but a significantly lower percent of SV segments narrowed 0 to 25% in XSA ($p < 0.05$) (Fig. 8).

Relation of amounts of saphenous vein narrowing to age: The relation between patient age and various

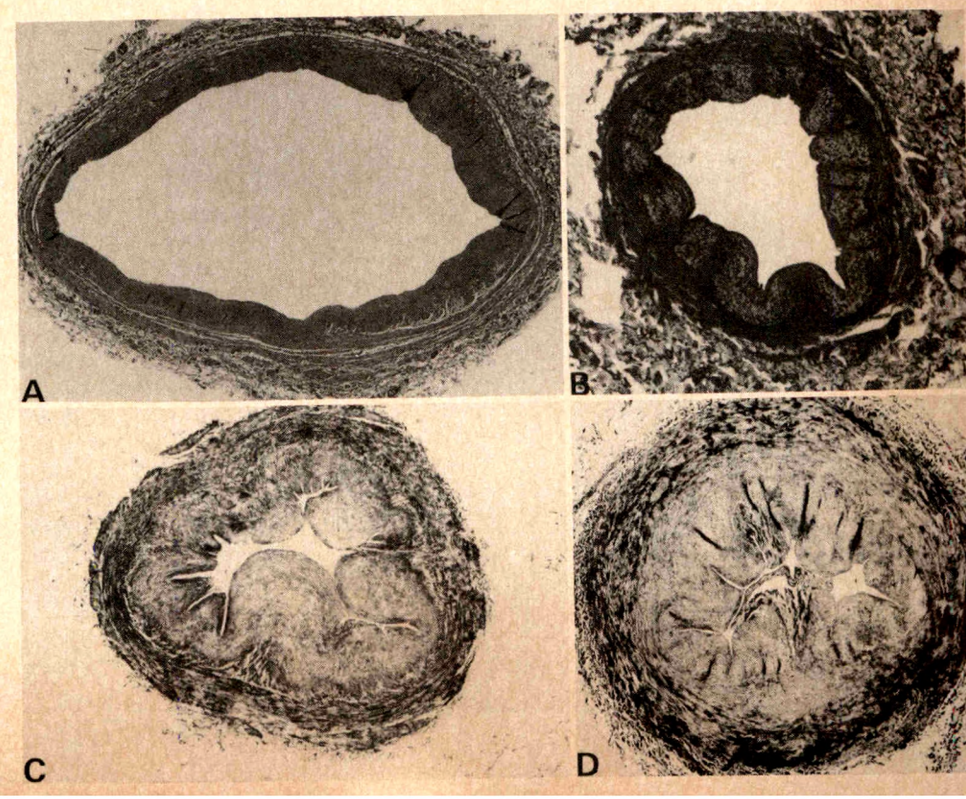

FIGURE 4. Photomicrographs of histologic sections of the 4 saphenous vein remnants illustrated in Figure 3. Movat stain.

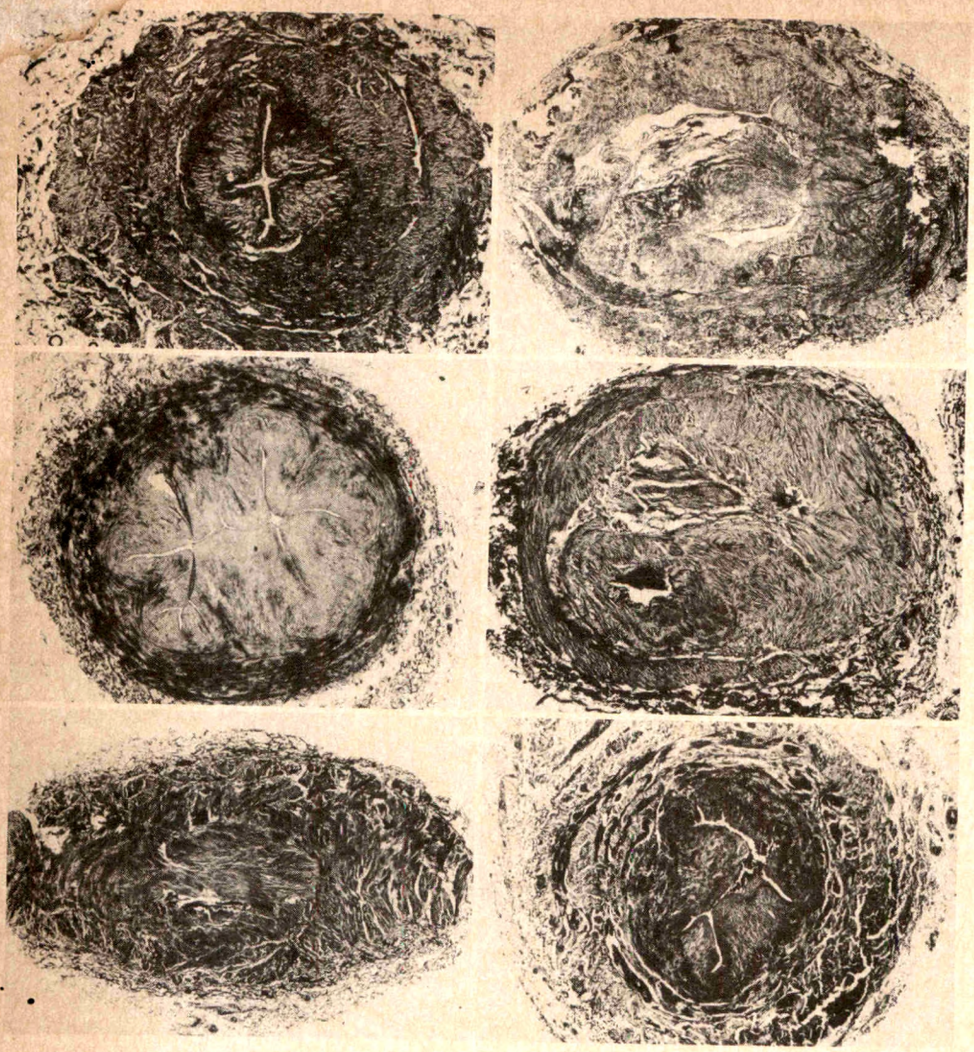

FIGURE 5. Photomicrographs of sites of maximal narrowing in saphenous vein remnants from 6 patients undergoing bypass operation (S79-162, S79-165, S81-63, S81-71, S81-175 and S81-202). All 6 remnants have severe luminal cross-sectional area narrowing by intimal fibrosis. Movat stain.

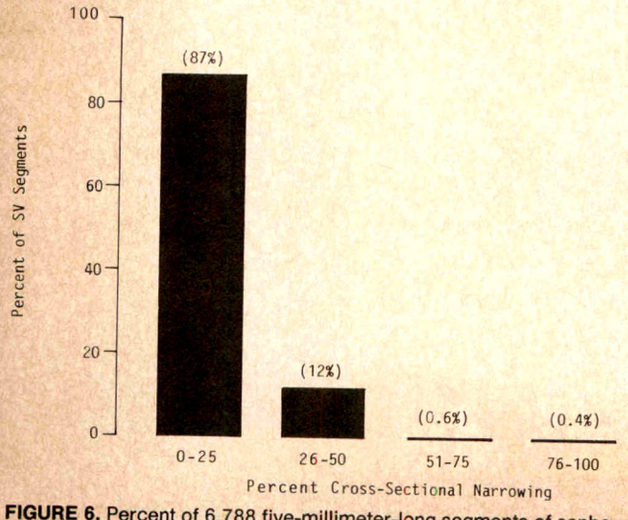

FIGURE 6. Percent of 6,788 five-millimeter-long segments of saphenous vein (SV) remnant from 402 patients undergoing aortocoronary bypass operation, narrowed to various degrees in cross-sectional area by intimal fibrosis.

amounts of luminal XSA narrowing is summarized in Table I and in Figure 9. Of 1,541 SV segments from 93 patients aged 50 years and younger, 8 (0.5%) segments were narrowed 76 to 100% in XSA by intimal fibrous tissue, compared with 8 (0.1%) of 5,247 segments from 309 patients aged older than 50 years. Analysis of luminal narrowing by age decade (Table I, Fig. 9) disclosed a similar frequency of severe (>75% XSA) narrowing between the fourth and seventh decades. No patient in the eighth decade of life had severe (>75% XSA) SV remnant luminal narrowing.

Relation of amount of saphenous vein luminal narrowing to sex and age: Analysis of SV remnants disclosed a similar frequency of severe luminal narrowing in men (7 of 1,392 [0.5%]) and women (1 of 149 [0.7%]) aged 50 years and younger and a similar frequency in men (6 of 4,186 [0.1%]) and women (2 of 1,061 [0.2%]) aged 50 years and older (Fig. 10).

Varicosity of saphenous vein remnants: Of 402 patients, 20 (5%) had focally or diffusely dilated SV remnants. The wall of the SV at sites of dilation were

TABLE II Comparison of Number of Segments and Percent Cross-Sectional Area Narrowing by Intimal Fibrosis in Saphenous Vein Aortocoronary Bypass Grafts and Their Respective Unused Saphenous Vein Remnants in 17 Necropsy Patients Dying Within 1 Day of Bypass Operation

No.	Age (yr) & Sex	Interval (days) Op → D	Length (cm) of SV		Total 5-mm SV Seg		No. (%) of Seg and XSA Narrowing by Intimal Fibrosis							
							0–25		26–50		51–75		76–100	
			G	R	G	R	G	R	G	R	G	R	G	R
1	34M	OR	22	6	44	12	40 (91)	10 (83)	4 (9)	2 (17)	0	0	0	0
2	40M	0.5	7.5	8	13	16	11 (85)	14 (88)	2 (15)	2 (12)	0	0	0	0
3	40F	OR	30	9	60	18	50 (83)	13 (72)	10 (17)	5 (18)	0	0	0	0
4	42M	OR	12	9	24	18	24 (100)	18 (100)	0	0	0	0	0	0
5	47F	1	9	14	18	28	18 (100)	27 (96)	0	1 (4)	0	0	0	0
6	49M	OR	21	11	42	22	38 (90)	19 (86)	4 (10)	3 (14)	0	0	0	0
7	56F	OR	12	17	24	34	20 (83)	27 (79)	4 (17)	7 (21)	0	0	0	0
8	56M	1	22	7	44	14	40 (91)	14 (100)	4 (9)	0	0	0	0	0
9	57M	OR	21	10	42	20	35 (83)	15 (75)	7 (17)	5 (25)	0	0	0	0
10	57M	OR	29	5	58	10	58 (100)	10 (100)	0	0	0	0	0	0
11	59M	OR	20.5	16	41	32	41 (100)	32 (100)	0	0	0	0	0	0
12	60M	OR	29.5	12	59	24	59 (100)	24 (100)	0	0	0	0	0	0
13	60M	OR	26	7	52	14	52 (100)	14 (100)	0	0	0	0	0	0
14	61F	OR	20.5	9	41	18	39 (95)	18 (100)	2 (5)	0	0	0	0	0
15	62M	1	16	11	32	22	32 (100)	21 (95)	0	1 (5)	0	0	0	0
16	64M	OR	13	10	26	20	24 (92)	19 (92)	2 (8)	1 (5)	0	0	0	0
17	68F	OR	17	8	34	16	34 (100)	15 (94)	0	1 (6)	0	0	0	0
Total range (Avg) 34–68 (54)	12M 5F	0–1 (0.2)	327 (19)	169 (10)	654	338	615 (94%)	310 (92%)	39 (6%)	28 (8%)	0	0	0	0

Avg = average; D = death; G = aortocoronary bypass graft; Op = operation; OR = operating room; R = remnant of excised SV; 0 = none; other abbreviations as in Table I.

thinner than normal in 16 patients and thicker than normal in 4 patients.

Discussion

Fibrous thickening of lumens of SV grafts studied early after CABG generally has been regarded as an acquired change rather than as a preexisting preoperative occurrence.[2–5,7] In the present study, analysis of unused portions of operatively excised SV disclosed varying degrees of intimal fibrous thickening in over 90% of SV segments before their use for CABG. Of 402 patients studied, the luminal narrowing was severe (>75% XSA) in 10 patients (16 segments [0.4%]) with near-total occlusion of segments from 7 patients.

Although intimal fibrous thickening is a common finding in the SV used as an aortocoronary conduit for more than 1 month,[2–5,7] considerable variation in amounts of intimal thickening is observed in grafts in

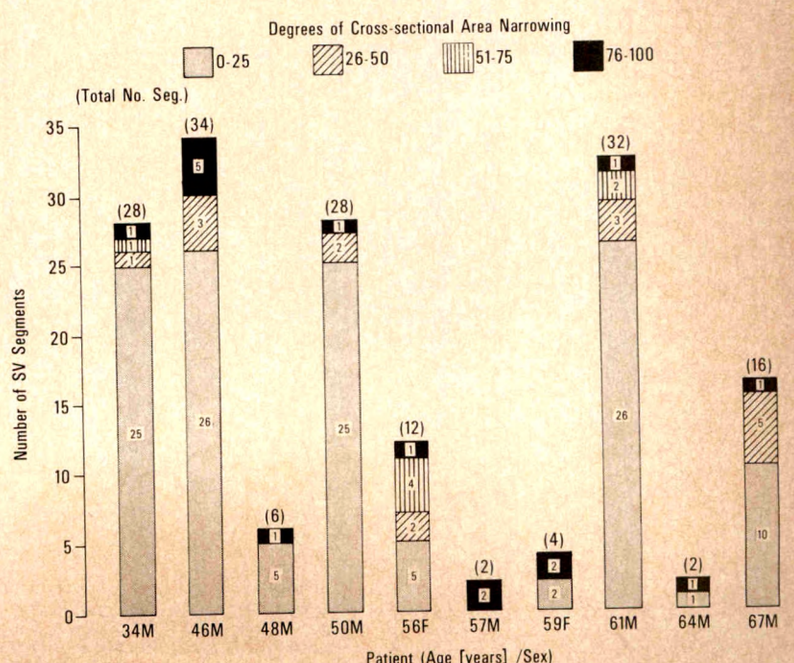

FIGURE 7. The variability in luminal cross-sectional area narrowing within the same saphenous vein (SV) remnant from the 10 patients having at least 1 five-millimeter SV segment (Seg.) narrowed 76 to 100% in cross-sectional area by intimal thickening.

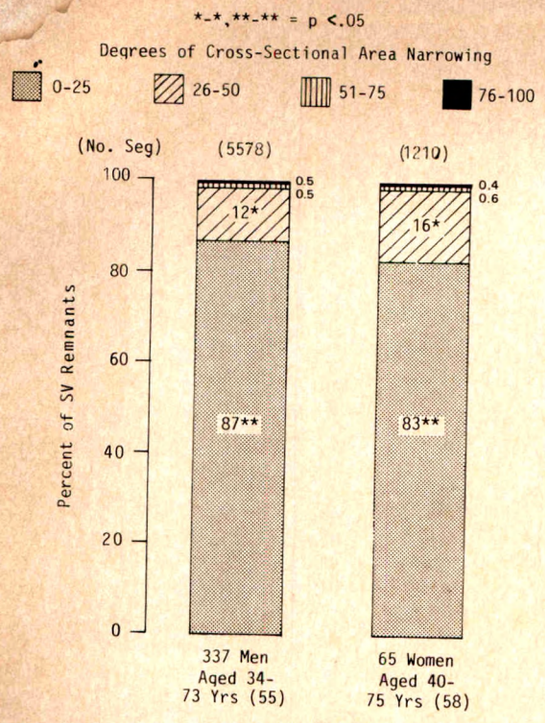

FIGURE 8. Relation between sex and degrees of cross-sectional area luminal narrowing by intimal fibrosis in 6,788 five-millimeter segments (Seg) of saphenous vein (SV) remnant from 337 men and 65 women who underwent aortocoronary bypass grafting.

place for a similar length of time. The variability in degree and extent of the luminal narrowing among different patients has been attributed to such factors as differing systemic arterial pressures,[4] vein damage during SV excision or manipulation before implantation,[21,22] and vein damage from agents used in preparation of the SV for implantation.[23] The high frequency of fibrous thickening in unused SV in the present study, and a similar distribution of these changes in remnant SV segments and their corresponding aortocoronary bypass graft segments suggests that preexisting intimal fibrous thickening may account for some of the variability. Preexisting severe narrowing of the SV used as a conduit of course may impede graft flow.

Two previous studies[18,20] have commented on morphologic changes observed in excised SV intended for use as aortocoronary bypass grafts. Cheanvechai et al[18] examined "representative pieces" of SV not used for grafting procedures from 1,179 patients undergoing CABG. Of 1,179 SV segments, 861 (73%) were "normal" and 318 (27%) were "abnormal." Of the 318 abnormal veins, 280 (88%) were "mildly phlebosclerotic" and 38 (12%) were "moderately sclerotic." Of the 1,170 patients, 391 underwent postoperative conduit angiography 1.5 to 24 months after operation (295 patients with normal SV remnants, 86 patients with abnormal SV remnants); no significant differences were observed in graft patency rates, graft stenoses, or luminal irregularities between the 2 groups. They concluded that the phlebosclerotic vein could be used as a bypass conduit without adverse results. Their study, however, did not define "mild" or "moderate" amounts of phlebosclerosis, and it did not correlate changes in unused (nonimplanted) segments of SV with those in used (implanted) segments.

Thiene et al[20] examined SV from 150 consecutive patients who underwent CABG. Intimal fibrous thickening was observed in 93%, but it was rarely severe enough to narrow the lumen more than 50% (unit not stated). These investigators graded amounts of intimal sclerosis as 1 to 4 with grade 4 representing luminal narrowing greater than 50%. Of 150 veins, 105 (70%) had intimal fibrous thickening but no SV segment had more than 50% luminal narrowing.

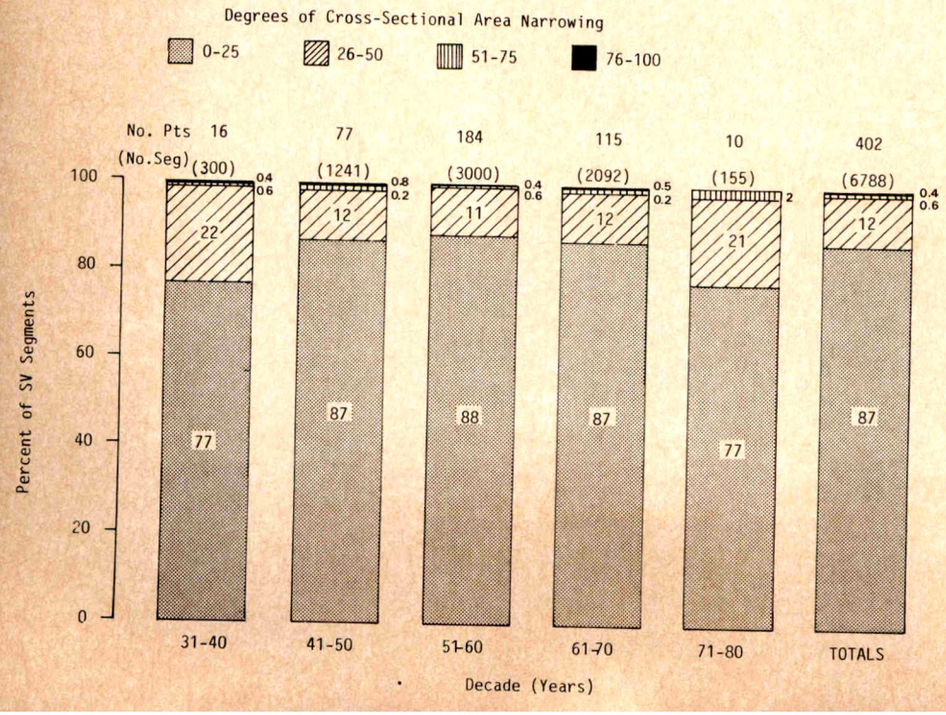

FIGURE 9. Relation between age and degrees of cross-sectional area luminal narrowing by intimal fibrosis in 6,788 five-millimeter segments (Seg) of saphenous vein (SV) remnant from 402 patients aged 31 to 75 years (mean 56) who underwent aortocoronary bypass grafting.

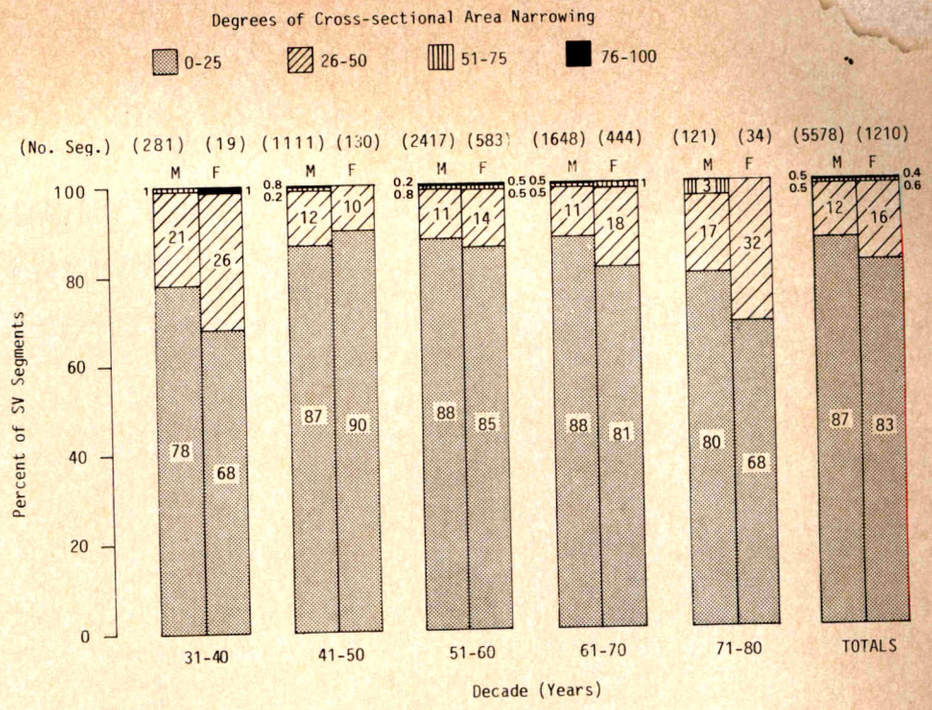

FIGURE 10. Relation between sex, age and degrees of cross-sectional area luminal narrowing by intimal fibrosis in 6,788 five-millimeter segments (Seg.) of saphenous vein (SV) remnants from 402 patients who underwent aorto-coronary bypass grafting.

Saphenous vein intimal fibrous thickening has been stated to increase with advancing age and to occur more frequently in women.[24] In our study and in the study by Thiene et al,[20] age did not correlate with the amount of intimal fibrous thickening. Furthermore, in the present study, severe (>75% XSA) intimal fibrous thickening was similar in both men and women.

About 5% of SV remnants examined in our study had varicoses. Although focal aneurysmal dilation of an implanted aortocoronary SV bypass graft has been reported,[25] its rarity suggests that focal graft aneurysm formation probably represents focal varicoses of the SV present at the time of graft insertion.

Of our 402 patients who underwent CABG, nearly 3,500 cm of SV (about 8.5 cm per patient) was not implanted. The length of unused SV ranged from 0.5 to 52 cm per patient; 45 patients (11%) had at least 15 cm of remnant vein. Repeat CABG is increasing and, correspondingly, the need for additional autogenous bypass graft material is increasing. Perhaps unused excised SV could be "stored" for future use in the same patient, or "denatured" and used as homologous bypass grafts in patients with depleted or diseased SV systems.

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Chronic Lorcainide Therapy for Symptomatic Premature Ventricular Complexes: Efficacy, Pharmacokinetics and Evidence for Norlorcainide Antiarrhythmic Effect

R. HARDWIN MEAD, MD, DEBORAH L. KEEFE, MD, ROBERT E. KATES, PhD, and ROGER A. WINKLE, MD

Chronic premature ventricular complexes (PVCs) have been effectively suppressed by oral lorcainide as reported in previous short-term studies. The plasma level-effect relation of lorcainide may be affected by the possible cardioactivity of norlorcainide, a metabolite that accumulates after repeated oral doses. This study evaluated the long-term efficacy of lorcainide in suppressing chronic symptomatic PVCs, and examined the relation of arrhythmia suppression to plasma concentrations of lorcainide and norlorcainide. Fourteen patients were treated with lorcainide, 200 to 400 mg/day, 12 of whom achieved nearly complete suppression of arrhythmias after treatment for 1 year. Chronic lorcainide treatment was well tolerated; no patient discontinued treatment because of adverse effects. Lorcainide and norlorcainide plasma concentrations remained stable after the first week of therapy. Antiarrhythmic activity persisted throughout the year. Upon drug withdrawal, the mean lorcainide washout half-life was 14.3 ± 3.7 hours and the mean norlorcainide washout half-life was 31.9 ± 8.9 hours. The return of arrhythmias occurred well after the lorcainide plasma concentration had decreased to subtherapeutic levels, suggesting an antiarrhythmic effect of norlorcainide. Thus, long-term lorcainide therapy is effective in treating chronic symptomatic PVCs and is well tolerated by most patients. The metabolite norlorcainide appears to have antiarrhythmic activity independent of lorcainide.

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Lorcainide is a new antiarrhythmic agent undergoing clinical investigation. In vitro studies demonstrate that it is a class I antiarrhythmic agent that decreases phase 0 of the action potential, slows conduction velocity and prolongs the effective refractory period.[1] In clinical trials, lorcainide effectively suppressed chronic ventricular ectopic activity[2–4] and ventricular tachycardia,[6–8] and had a marked negative dromotropic effect on the accessory pathway in patients with Wolff-Parkinson-White syndrome.[5] Intracardiac conduction times and atrial and ventricular refractoriness were prolonged after intravenous or short-term oral loading.[9,10]

Short-term studies have revealed a marked saturable first-pass hepatic metabolism of lorcainide, with accumulation of a metabolite, norlorcainide.[11–13] Bioavailability was low after single, oral, 100-mg doses, but increased with higher doses and approached 100% after several days of multiple oral dosing.[6,11] Norlorcainide accumulated after multiple oral doses, but not after multiple intravenous doses.[11] Within several days of multiple dosing, norlorcainide plasma concentrations exceeded those of lorcainide, and the norlorcainide concentration reached steady state after approximately 1 week of therapy.[14] Norlorcainide has a disappearance half-life of approximately 3 times that of lorcainide after short-term oral therapy, with plasma concentrations more than twice that of the parent compound.[12] The plasma level-effect relation of lorcainide is confounded by the cardioactivity of norlorcainide, which was shown in 1 patient to have antiarrhythmic efficacy; this may explain why some patients have responded to oral but not intravenous lorcainide therapy.[14]

Most studies have focused on the acute or short-term effects of lorcainide. We evaluated the long-term efficacy and patient tolerance of lorcainide in patients with chronic symptomatic ventricular ectopic activity, and correlate suppression of arrhythmias with plasma concentrations of both lorcainide and norlorcainide.

From the Division of Cardiology, Stanford University School of Medicine, Stanford, California. Manuscript received July 2, 1984; revised manuscript received September 7, 1984, accepted September 10, 1984.

Address for reprints: R. Hardwin Mead, MD, 770 Welch Road, Palo Alto, California 94304.

Methods

Patients: Fourteen patients (10 men, 4 women, mean age 55 years) with symptomatic, chronic premature ventricular complexes (PVCs) responsive to lorcainide during short-term evaluation[12] were studied. Patients were excluded if they had myocardial infarction within 3 months, syncope, sustained ventricular tachycardia or a history of ventricular fibrillation, high degrees of atrioventricular or bifascicular block, uncontrolled congestive heart failure, renal or hepatic disease, or uncontrolled systemic hypertension.

Patient characteristics: Three of the 14 patients included in the study had no known structural heart disease; 2 had mitral valve prolapse. Seven patients had known coronary artery disease, 3 with previous myocardial infarctions; 1 patient had hypertensive heart disease without documented coronary disease; and 1 patient had cardiomyopathy due to acromegaly. All patients had poor results with at least 1 conventional antiarrhythmic drug before lorcainide therapy. No patient was taking cimetidine.

Study design: All patients had 2 separate 24-hour ambulatory electrocardiographic (ECG) recordings while not taking antiarrhythmic drugs. All antiarrhythmic medications had been discontinued for at least 5 half-lives to assume adequate washout. No patient had previously received amiodarone. Twenty-four-hour ambulatory ECG recordings were repeated at 1 week, 1 month and 2 months, and then every 2 months, for a total of 12 months. Each patient began therapy with 100 mg orally every 12 hours; the dose was increased as needed based on the results of the ambulatory ECG recordings. After 12 months, the drug was discontinued. Twenty-four-hour outpatient ambulatory ECG recordings were performed continuously during the 10 days after therapy was discontinued. Adverse effects were recorded in detail.

Determination of plasma lorcainide and norlorcainide concentrations: Samples of venous blood (10 ml) were obtained by direct venipuncture, or through an indwelling intravenous catheter, at the beginning of each monitoring period. Plasma was drawn for drug concentration determination during the drug withdrawal period just before the last dose, and then at 1, 2, 3, 4, 6, 8, 10, 12, 24 and 36 hours after cessation of therapy, and then daily for 10 days. These were placed into heparinized screw-cap tubes, centrifuged, and the plasma frozen at −20° C until analyzed. Analysis was performed as previously reported by a high-pressure liquid chromatographic method that detects both lorcainide and its N-dealkylated metabolite, norlorcainide.[15]

Data analysis: Ambulatory electrocardiograms were analyzed by the Stanford computer-assisted method, which gives accurate counts of all ventricular arrhythmias occurring on each recording. Total PVC counts, as well as counts of all pairs and runs, were recorded for the entire 24 hours. Counts were normalized to 24 hours for tapes not exactly 24 hours long.

Mean steady-state lorcainide and norlorcainide levels were determined during the last dosing interval by dividing the area under the plasma-concentration time curve by the duration of the dosing interval. The plasma-concentration time curve was determined by the trapezoidal rule. The disappearance half-lives were determined by linear least-squares fitting of the terminal log-linear portion of the plasma concentration-time curve during the washout period.

Data are presented as mean ± standard deviation, and statistical comparisons of the washout half-life were determined with the Student t test for paired data.

Results

Chronic antiarrhythmic efficacy: Lorcainide was effective for chronically suppressing PVCs in 12 of the 14 patients entered into the study. Patient 5, initially believed to be responding to lorcainide, had severe sleep disturbance and did not have a reduction in his arrhythmias after 1 month of therapy with lorcainide, and was withdrawn from the study. Patient 6 was noncompliant with his medications and was withdrawn at 3 months. Inadequate control of PVCs occurred in patients 4, 10, 11 and 13 while receiving lorcainide, 100 mg twice daily. Increasing the daily dose to between 250 and 400 mg resulted in satisfactory suppression of arrhythmias. The doses taken by each patient are summarized in Table I.

TABLE I Mean Lorcainide and Norlorcainide Steady-State Concentrations 1 Month Through 12 Months

Pt	Dose (mg) (bid)	Lorcainide (ng/ml)	Norlorcainide (ng/ml)
1	100	57 ± 15	177 ± 64
2	100	138 ± 36	352 ± 102
3	100	77 ± 28	279 ± 55
4	100*	366 ± 234	732 ± 452
7	100	158 ± 22	252 ± 31
8	100	212 ± 30	376 ± 70
9	100	342 ± 162	434 ± 146
10	150	288 ± 28	1040 ± 146
11	125	92 ± 49	404 ± 101
12	100	346 ± 47	578 ± 69
13	200	400 ± 76	1075 ± 263
14	100	74 ± 42	103 ± 38
Mean ± SD		212 ± 129	483 ± 316

* Patient 4 took 100 mg 3 times daily.
Values are mean ± standard deviation.

The 12 patients who completed the study showed a marked reduction in arrhythmias (Fig. 1). No patient had syncope or sustained ventricular tachycardia during the year of therapy. The antiarrhythmic effect of lorcainide persisted in all patients, although patient 9 had an increase in the frequency of arrhythmia during the last month of the study. This patient had a significant increase in his arrhythmias during the washout phase of the study when compared with the period before drug administration, which may account for the apparent diminution in lorcainide efficacy.

Plasma concentration of lorcainide and norlorcainide: The mean plasma concentrations of lorcainide and norlorcainide measured at the time of each ECG monitoring period are listed in Table I. For patients in whom the lorcainide dose was changed during the study period, the values represent the levels obtained when the effective dose had been achieved. The mean plasma lorcainide concentration ranged from 57 to 400 ng/ml (average 212 ± 129) in these patients. The mean plasma norlorcainide concentrations ranged from 103 to 1,075 ng/ml (average 483 ± 316). The mean individual coefficient of variation for the plasma lorcainide concentration in each patient was 32 ± 19%; for norlorcainide it was 27 ± 14%. Coefficients of variation for the mean lorcainide and norlorcainide concentrations for the entire group were 61% and 65%, respectively. The variations in plasma concentration in each patient were thus significantly less than the variation between patients.

Mean steady-state plasma lorcainide and norlorcainide concentrations were determined for 10 patients during 1 dosing interval after 1 year of therapy. The mean plasma lorcainide concentration during this dosing interval ranged from 44 to 287 ng/ml (mean 171 ± 73) and the mean norlorcainide plasma concentration ranged from 103 to 889 ng/ml (mean 387 ± 225). The ratio of norlorcainide to lorcainide varied from 1.1 to 4.1 (average 2.4 ± 1.0). In addition, for the 8 patients who received 100 mg twice daily, there was a strong negative correlation between the concentration of lorcainide and the ratio of norlorcainide to lorcainide ($r = -0.63$).

After 1 year of lorcainide therapy, 12 patients were available to participate in the washout phase, at which time the drug was withheld for 10 days. Patient 13 was fearful of the palpitations that developed from her arrhythmia; therefore, lorcainide was not discontinued. Patient 7 self-administered several lorcainide doses during the washout period, and thus was not included. The half-lives of lorcainide and norlorcainide determined during the washout period in the remaining 10 patients are listed in Table II. The half-life of lorcainide in these patients ranged from 10.7 to 22.7 hours (average 14.3 ± 3.7). Norlorcainide half-lives ranged from 19.2 to 47.7 hours (average 31.9 ± 8.9). In 6 patients, washout half-lives had been determined after only 4.5 days of therapy.[12] For these 6 patients, the lorcainide half-lives varied from 6.2 to 13.5 hours (mean 10.8 ± 2.9) and the norlorcainide half-lives ranged from 19.1 to 37.6 hours (mean 28.9 ± 8.4) at 4.5 days. Although there was no difference in the norlorcainide half-life at 4.5 days and 1 year of therapy, the increase in the lorcainide half-life over the year was significant ($p < 0.05$).

Return of arrhythmias after drug withdrawal: relation to plasma drug concentration: Lorcainide therapy was successfully withdrawn in 10 patients, as previously noted. Tables III and IV show the return of arrhythmias in these patients. In patient 14, arrhythmias did not return during the washout period. In the remaining patients, there was a gradual return of ventricular arrhythmias, with up to 6 days elapsing before 24-hour monitoring revealed a full return of PVCs, pairs and runs. The return of arrhythmias relative to the plasma drug concentrations for patients 1 and 3 is shown in Figures 2 and 3. The lorcainide plasma concentration was below 35 ng/ml by day 3 in all patients except patient 12, in whom it was 76 ng/ml.

Adverse effects: Adverse effects were frequent during chronic lorcainide therapy; all patients reported at least 1 adverse effect during the year. Sleep disturbances were the most common adverse effect, occurring in 9 patients during the first week of treatment and persisting to some extent in 7 patients by the end of 1 year. Four of the 9 patients used flurazepam to minimize the sleep disturbance during the first month of treatment, and 2 of these patients continued to use the medication occasionally after the first 2 months. Gastrointestinal upset, headache, and a sense of anxiety or

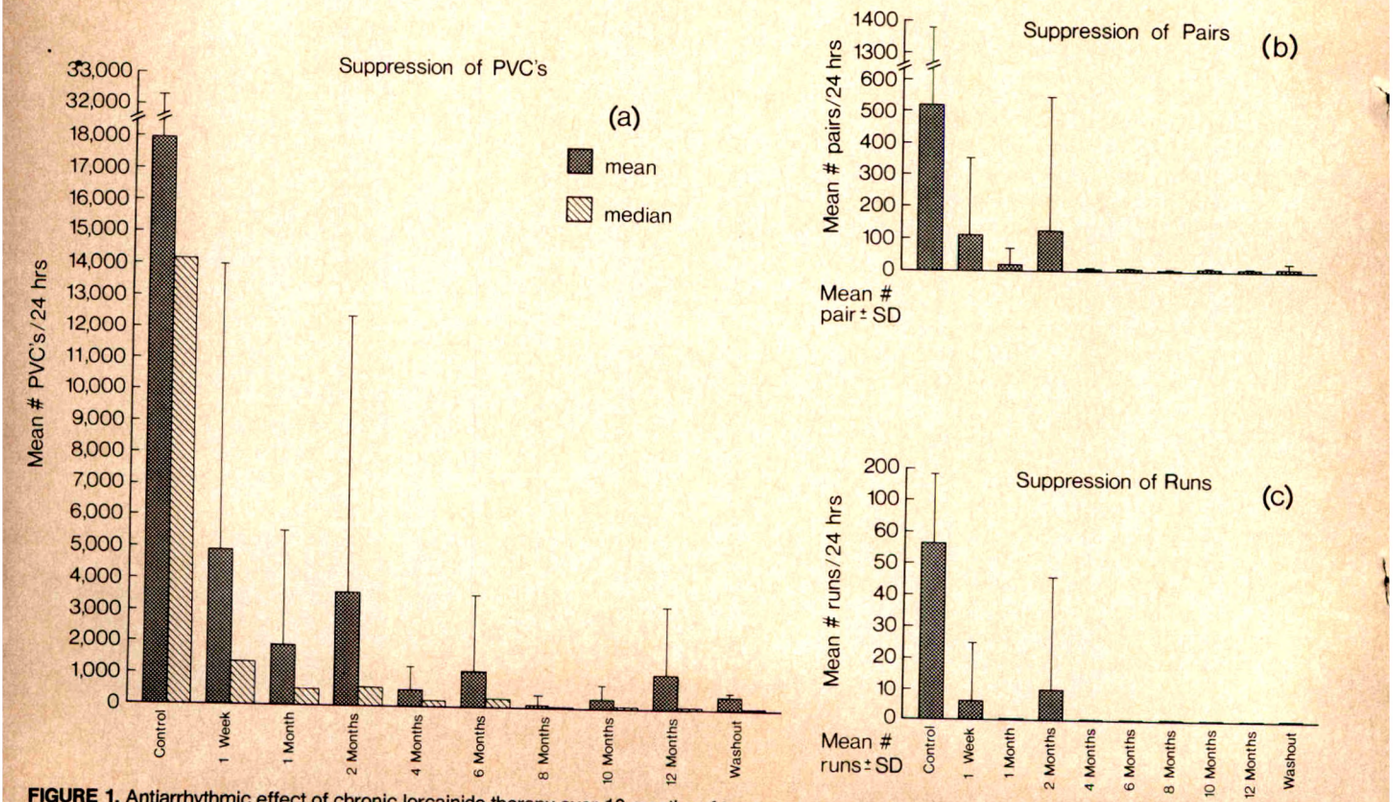

FIGURE 1. Antiarrhythmic effect of chronic lorcainide therapy over 12 months of treatment compared with baseline arrhythmia frequency. Suppression of premature ventricular complexes (PVCs) (**a**), pairs, (**b**) and runs (**c**) persisted during the year of therapy. SD = standard deviation.

TABLE II Lorcainide and Norlorcainide Elimination Half-Lives

Pt	Washout Half-Life 1 Year (hours)		Washout Half-Life 4.5 Days (hours)	
	Lorcainide	Norlorcainide	Lorcainide	Norlorcainide
1	12.3	28.5	...	...
2	12.3	36.8	...	...
3	10.7	34.8	...	...
4	12.3	41.7	...	...
8	10.8	33.3	9.5	35.2
9	16.9	24.1	11.4	24.5
10	22.1	47.7	13.2	36.4
11	16.3	22.4	6.6	19.1
12	...	19.2	6.2	20.7
14	15.5	30.1	13.5	37.6
Mean	14.3 ± 3.7 (16.3 ± 4.0)*	31.9 ± 8.9 (29.5 ± 10.3)†	10.8 ± 2.9*	28.9 ± 8.4†

* $p < 0.05$.
† p = not significant.
... = not determined.
Values in parentheses represent means for patients also studied at 4.5 days.

tremulousness were also reported by several patients, although these effects subsided during the months of therapy (Table V). Despite the high incidence of adverse effects, no patient was withdrawn from treatment solely because of adverse effects of lorcainide. Patients who reported sleep disturbance did not have daytime somnolence or fatigue, and several reported a sense of increased energy. Four patients reported the new onset of fatigue and sleepiness beginning 2 to 5 days after lorcainide was discontinued, which was unrelated to prior sleep disturbance or flurazepam use. This "rebound hypersomnolence" persisted throughout the withdrawal period in these patients.

Discussion

Previous studies have shown that lorcainide is an effective antiarrhythmic agent in patients with frequent PVCs receiving short-term oral treatment regimens and in double-blind comparison with placebo.[2,3] Myburgh et al[16] showed a sustained antiarrhythmic effect over 6 months in 20 patients after myocardial infarction treated with 200 mg/day of lorcainide. This study demonstrates the long-term efficacy of lorcainide in patients with varying cardiac disorders underlying their frequent ectopy. Dosage adjustments were required in 4 of our patients to attain a complete therapeutic response, but the antiarrhythmic effect persisted over the year of treatment, since arrhythmias returned in all but 1 patient in whom the drug treatment was withdrawn.

With chronic oral lorcainide therapy, the plasma concentration of norlorcainide exceeded that of lorcainide; the average norlorcainide/lorcainide ratio of 2.4 was similar to that reported in short-term oral treatment studies.[12] The negative correlation between the lorcainide concentration and the norlorcainide/lorcainide ratio suggests that those patients with more active first-pass metabolism have lower plasma lorcainide levels and produce relatively higher amounts of norlorcainide. The plasma concentrations measured throughout the year, and the mean steady-state levels, are also in agreement with previous studies,[12,13] and did not change significantly over the year in patients receiving therapy. While a considerable variation occurred in the elimination half-lives of both compounds, the mean lorcainide elimination half-life of 14.3 hours is

TABLE III Return of Premature Ventricular Complexes (PVCs) During Drug Washout

Pt	PVCs Per 24 Hours									
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
1	8	8	271	2,751	6,450	14,020	10,051	16,707	12,950	15,028
2	8	1	2	15	52	634	219	12	352	100
3	28	97	226	651	1,179	1,305	1,290	1,473	1,410	2,141
4	768	2,453	6,147	5,937	5,460	6,801	7,424	13,866	13,899	16,049
8	7	97	847	3,835	3,787	1,407	3,822	940	...	4,509
9	4,075	23,527	27,186	23,735	...	16,847	24,406	22,721	...	...
10	72	1,614	2,745	2,033	1,319	7,842	7,044	5,330	4,008	7,125
11	1	169	8,555	21,369	18,036	25,907	14,003	9,667	19,894	26,394
12	0	0	175	1,969	2,035	2,026	3,275	2,115	4,463	6,067
Median	8	97	847	2,751	2,909	6,801	7,044	5,330	4,463	6,596
	Mean Concentration Lorcainide and Norlorcainide (ng/ml)									
L	135 ± 71	78 ± 60	25 ± 21	7 ± 10	1 ± 1	0	0	0	0	0
NL	347 ± 115	406 ± 213	310 ± 185	189 ± 113	125 ± 85	84 ± 76	48 ± 51	26 ± 32	20 ± 32	11 ± 20

L = lorcainide; NL = norlorcainide; ... = not determined.

TABLE IV Return of Pairs and Runs During Washout

Pt	Premature Ventricular Complexes Per 24 Hours									
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
1	0/0	0/0	0/0	4/0	0/0	2/0	4/0	12/1	2/0	7/0
2	0/0	0/0	0/0	0/0	0/0	0/0	1/0	0/0	0/0	0/0
3	0/0	0/1	0/0	1/0	0/0	2/0	4/0	3/0	2/0	7/0
4	0/0	3/0	27/2	7/0	37/1	92/3	124/1	364/4	275/3	441/1
8	1/0	0/0	0/0	4/0	4/0	3/0	3/0	1/0	...	44/0
9	97/1	1149/122	722/103	339/141	...	826/101	941/160	1186/135	...	...
10	1/0	73/0	63/3	138/6	138/3	883/119	819/86	361/143	305/113	592/195
11	0/0	0/0	5/1	88/58	158/47	446/168	209/106	139/43	353/145	592/195
12	0/0	0/0	0/0	0/0	0/0	1/0	0/0	0/0	0/0	2/1

Values represent number of pairs per runs per 24 hours.
... = not determined.

longer than reported in other studies and is similar to the 17 hours reported for patients with congestive heart failure.[6,9,12] A significant increase in the lorcainide elimination half-life also occurred in a portion of these patients, when compared with that in the first week of therapy. Lorcainide clearance is highly dependent on hepatic blood flow,[9] and this could explain the prolonged elimination half-life in patients with congestive heart failure. Our patients did not exhibit evidence of heart failure, and this is an unlikely mechanism for the observed increase in elimination half-life. A changing volume of distribution of lorcainide would be unlikely also. In patients in whom the elimination half-life was determined at 4.5 days of treatment, plasma lorcainide concentrations were less than those obtained during the subsequent year of therapy. The mean concentration at 1 week was 82 ± 68 ng/ml for the 4 patients in whom it was determined and who also had lorcainide elimination half-life determined at 1 year. This finding would suggest that the observed increase in elimination half-life is due to a decrease in lorcainide clearance, which may continue to develop after 4.5 days of treatment. The presystemic hepatic clearance of oral lorcainide is saturable,[11] and the change in lorcainide clearance observed here may be due to a prolonged time to saturation of first-pass metabolism. If this is coupled with the long half-life of the drug, more than 4.5 days may be required to achieve an initial steady-state metabolism, which would then explain the apparent change in clearance with long-term oral dosing.

The long elimination half-life of norlorcainide enabled us to examine its antiarrhythmic activity during the washout period, because high norlorcainide concentrations were still present after lorcainide concentrations had fallen below the therapeutic range. Comparison of lorcainide and norlorcainide plasma concentrations with return of arrhythmias strongly suggests an antiarrhythmic effect of norlorcainide in

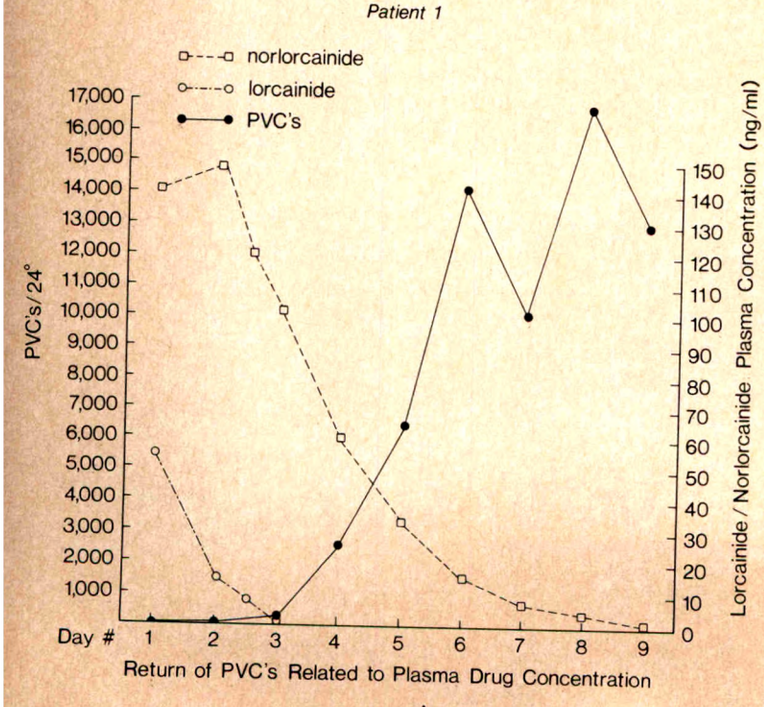

FIGURE 2. Return of premature ventricular complexes (PVCs) during drug washout in patient 1. An antiarrhythmic effect persisted for 4 days after cessation of therapy, when lorcainide plasma concentrations had fallen to subtherapeutic levels.

these patients. Klotz et al[14] reported efficacy of oral lorcainide in 2 patients who did not respond to the intravenous drug, suggesting a contribution of active metabolites to the antiarrhythmic effect. Meinertz et al[13] documented a marked antiarrhythmic effect of norlorcainide infused into 1 patient, in whom plasma concentrations were almost 1,000 ng/ml. The lower plasma lorcainide concentrations that result in effective oral treatment compared with the concentration needed with intravenous lorcainide also support a contribution of norlorcainide to the therapeutic efficacy of the oral drug. A similar observation was made with regard to encainide therapy, in which persistence of antiarrhythmic effect during drug washout suggested significant contribution of 1 or more of its metabolites to antiarrhythmic activity.[17] In this study, plasma levels of lorcainide were well below the previously established minimal effective concentrations of 150 to 400 ng/ml[9] by day 3 of drug washout. Because it is unlikely that these low lorcainide concentrations would be effective in this group, in which the average lorcainide concentrations were more than 200 ng/ml during the year, the persistence of an antiarrhythmic effect 72 hours or longer after the cessation of the drug is strong circumstantial evidence for norlorcainide activity.

The presence of a pharmacologically active metabolite with a long half-life has several therapeutic implications. Atrial and ventricular refractoriness increase, and the AH interval also increases in patients given oral lorcainide after an intravenous infusion.[10] This may reflect a time delay in the distribution of lorcainide to all parts of the myocardium, because much lower plasma concentrations of lorcainide are needed during the postinfusion period to achieve the degree of antiarrhythmic effect seen immediately after the infusion is given.[13] However, the changes seen only with oral lorcainide treatment may also be due to the presence of norlorcainide. Plasma concentrations of both compounds should be determined when drug levels are used to monitor electrophysiologic and antiarrhythmic effects of oral lorcainide. In addition, norlorcainide alone may prove to be a useful antiarrhythmic agent, and further studies to evaluate its actions and adverse effects are warranted. Finally, the persistence of the effect of norlorcainide for several days or longer should be considered if a patient is withdrawn from lorcainide and another antiarrhythmic agent begun.

TABLE V Adverse Effects of Oral Lorcainide Therapy

Adverse Effect	1 Week	6 mo	12 mo	Washout
Sleep disturbance	9	8	7	0
Vivid dreams	5	2	1	0
Inability to sleep	9	7	6	0
Night sweats	2	1	1	0
Anxiety/tremor	3	1	0	1
GI disturbance	5	3	1	0
Headache	3	1	1	0
Sleepiness/fatigue	0	0	1	4

GI = gastrointestinal.

The adverse effects of chronic lorcainide therapy were frequent, and sleep disturbances were the predominant adverse effects, as in previous reports.[2,8,18] We have shown that sleep fragmentation and decrease in total sleep time occurs during oral lorcainide therapy, but that daytime mood and alertness is not consistently affected.[18] Saksena et al[8] reported that in 12 patients with recurrent ventricular tachycardia who were treated

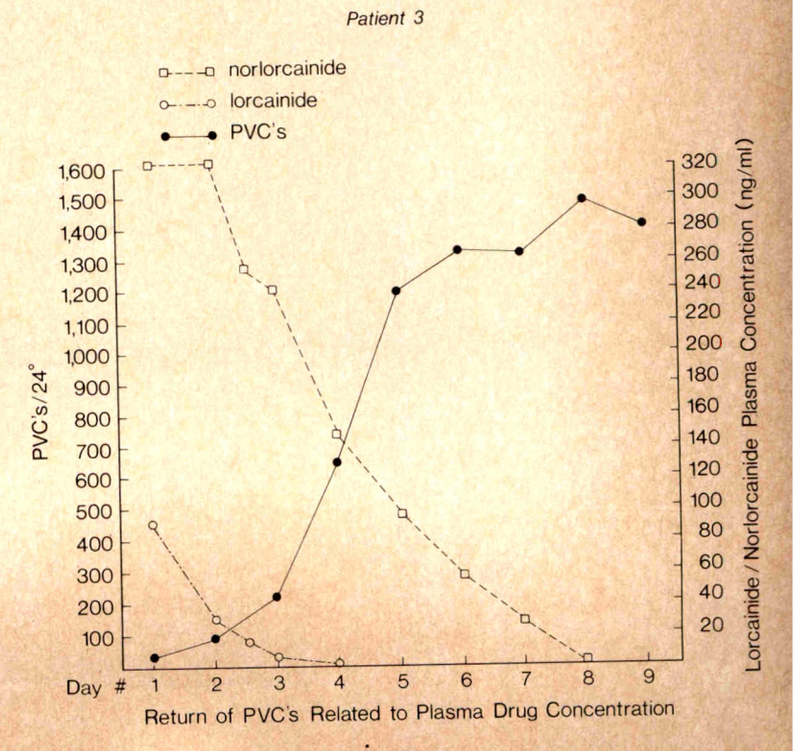

FIGURE 3. Return of premature ventricular beats (PVCs) during drug washout in patient 3. Lorcainide plasma concentration was below 40 ng/ml by day 2, yet ventricular arrhythmias did not return to the baseline frequency until day 5 of washout.

with oral lorcainide, 2 patients had sleep disturbances severe enough to withdraw from the study, and noted that long-term lorcainide therapy was severely limited by adverse effects. This is in contrast to our patients, most of whom had disturbed sleep, but we did not find this effect severe enough to warrant discontinuation of treatment. The "rebound hypersomnolence" observed in several patients on drug withdrawal also suggests the development of tolerance to the sleep disturbance with chronic lorcainide therapy. With the dosages we used, lorcainide was well tolerated in most patients, and therapy was not significantly hampered by its adverse effects.

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Flecainide: Long-Term Treatment Using a Reduced Dosing Schedule

DAVID FLOWERS, MD, DEBORAH O'GALLAGHER, RN, VILMA TORRES, MD, DENNIS MIURA, MD, PhD, and JOHN C. SOMBERG, MD

Flecainide was initially prescribed at a dose of 200 mg twice daily, but after early toxicity in patients with ventricular tachycardia (VT), the dosage was reduced to 100 mg twice daily. The effects of flecainide were studied in 40 patients (29 men and 11 women, mean age 62 ± 2 years, ejection fraction 45 ± 3%) who underwent programmed electrical stimulation to determine the efficacy of flecainide in preventing VT chronically at the reduced dose. Sustained VT was induced in 21 patients and nonsustained VT in 19. Flecainide prevented VT induction in 26 patients (65%). At a mean dose of 1.5 ± 0.1 mg/kg, prolongation occurred in the effective refractory period of the first (280 ± 5 vs 249 ± 5 ms) and second (254 ± 6 vs 209 ± 9 ms) extrastimuli ($p < 0.01$). In the patients protected by flecainide, the effective refractory periods increased by a 17 ± 2% and 21 ± 3%, in contrast to only a 7 ± 3% and 6 ± 4% increase in the nonprotected group ($p < 0.05$), despite a higher mean dose (1.9 ± 0.1 vs 1.35 ± 0.1 mg/kg). Twenty-one patients were discharged on flecainide therapy, 100 mg twice daily, and were followed for a mean of 11 months. Sixteen patients are alive and well, 1 died suddenly, 1 died from a noncardiac cause and 1 had a "breakthrough" arrhythmia. Two were switched to quinidine therapy by their referring physicians, but were without problems while receiving flecainide. Thus, flecainide therapy guided by programmed electrical stimulation is effective at a reduced dose.

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Flecainide acetate is an investigational antiarrhythmic agent developed by Barnitt et al.[1] The efficacy of flecainide for the control of ventricular premature contractions (VPCs) in outpatients has been reported.[2–9] Initial studies have demonstrated the use of flecainide in therapy guided by programmed electrical stimulation and have shown a correlation between acute drug testing with the intravenous form and subsequent protection from ventricular tachycardia (VT) in long-term follow-up.[10,11] In these clinical studies, a total daily oral dose of 300 to 600 mg has usually been given in a twice-daily regimen. Several recent reports have documented various toxic effects of flecainide, including death, that have occurred at these dosing schedules with serum levels ranging from 500 to 2,200 ng/ml.[12–15] Several investigators have suggested that a lower daily dose may be effective, while reducing the incidence of toxicity to a more acceptable level.[15] Forty patients who were referred to the cardiac arrhythmia service for PES-guided therapy because of VT underwent intravenous drug testing with flecainide. We report on the acute drug testing results and long-term follow-up using a reduced dosage regimen of 100 mg of flecainide administered twice daily.

From the Cardiac Arrhythmia Service, Departments of Medicine and Pharmacology, Albert Einstein College of Medicine, Bronx, New York. Manuscript received June 25, 1984; revised manuscript received and accepted August 20, 1984.

Address for reprints: John C. Somberg, MD, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Room 208 Forchheimer Building, Bronx, New York 10461.

Methods

All the patients were admitted to the coronary care unit 36 to 48 hours before PES studies. A baseline electrocardiogram (ECG), Holter ECG, x-ray, urinalysis, hematologic studies and chemistry profiles were performed. Each patient gave informed consent and PES was performed after the patient had discontinued taking all antiarrhythmic drug treatment for at least 5 half-lives.

During all the PES studies, before and after drug administration, surface electrocardiographic leads I, II, aVF and V_5 were continuously monitored, stored on 8-channel magnetic tape and printed on a polygraph recorder along with intracardiac recordings. These data were recorded using a Siemens Elema Mingograf at paper speeds of 25 and 100 mm/s during induction of VT. The intracardiac electrograms were filtered between 50 to 200 Hz and then amplified using a Bloom Associates amplifier.

After PES studies were complete, patients were observed in the coronary care unit for 48 hours and clinical laboratory

TABLE I Comparison of Electrophysiologic Measurements for All Patients Tested with Flecainide

	Mean BP (mm Hg)	HR (beats/min)	PR (ms)	QRS (ms)	QT (ms)	S_2 (ms)	S_3 (ms)
No therapy	94 ± 3	76 ± 3	169 ± 5	94 ± 4	386 ± 7	249 ± 5	208 ± 9
Flecainide (1.5 ± 0.1 mg/kg)	91 ± 3	73 ± 2	190 ± 5*	100 ± 4	400 ± 7	280 ± 5†	254 ± 6†

Significant difference from the group off therapy: * $p < 0.05$; † $p < 0.01$.
BP = blood pressure; HR = heart rate; S_2 = shortest interval from end of the pacing train that the first extrastimulus causes a ventricular depolarization; S_3 = shortest interval between the first and second extrastimulus that causes a ventricular depolarization after the second extrastimulus.

tests, 12-lead ECGs and physical examinations were repeated.

Flecainide was given intravenously by an intermittent bolus of 20 mg every 5 minutes to a dose of 1 mg/kg; the patient then underwent PES. If this dose was not protective, additional boluses were given to a total of 2 mg/kg and testing was repeated. Heart rate, blood pressure, PR, QRS and QT intervals were measured every 5 minutes. Drug administration was terminated if severe nausea or hypotension developed or if QRS or QT intervals were prolonged more than 50% over baseline values. Plasma levels were determined immediately after the PES testing.

PES was performed using a hexapolar pacing catheter introduced through the right internal jugular vein to the apex of the right ventricle. In patients in whom VT could not be induced from the right ventricular apex, the catheter was repositioned to the right ventricular outflow tract. A digital stimulator (Bloom Associates) was used to deliver square-wave electrical impulses of 2.0 ms in duration, with amplitude set at twice diastolic threshold. The right ventricle was driven with a pacing train of 6 beats at a cycle length of 500 ms, with an intertrain interval of 8 seconds.

Single premature ventricular stimuli (S_2) were delivered in late diastole starting at 500 ms from the end of the pacing train and progressively introduced earlier by 20-ms decrements. The shortest interval at which S_2 evoked a depolarization was termed the refractory period. The stimulus was brought out 10 ms further from the end of the pacing train, then a second extrastimulus was introduced at the sum of the S_1S_1 and S_1S_2 intervals and introduced at 20-ms decrements. This programmed introduction of premature stimuli was performed until VT (10 or more beats) was obtained or until 4 premature stimuli were introduced.

Nonsustained VT was defined as at least 10 beats of VT that terminated spontaneously and sustained VT was defined as VT that lasted 30 seconds or required either pacing techniques or defibrillation for termination. A patient was considered protected if 4 stimuli failed to induce more than 3 ventricular beats beyond the last extrastimulus.

Patients: Forty patients underwent electrophysiologic testing to determine if flecainide acetate was an effective antiarrhythmic agent. Twenty-nine were men and 11 were women, mean age 61 ± 2 years. The mean nuclear ejection fraction as determined by nuclear ventriculography performed before flecainide loading was 45 ± 3% (range 25 to 79%). Seven patients presented with a cardiac arrest, 1 patient had syncope with suspected VT as a cause (although not documented on Holter), 20 patients had symptomatic VT (VT associated with syncope, confusion, dizziness, angina or symptoms of congestive heart failure causing presentation at a hospital), and 12 had asymptomatic, nonsustained VT documented on the Holter monitoring. Twenty-nine patients had coronary artery disease, 1 patient had mitral valve prolapse, 2 had dilated cardiomyopathy, and 8 had no apparent structural heart disease detected by routine screening studies. They had failed an average of 1.9 ± 0.2 drugs clinically before being referred to the electrophysiology laboratory, although usually they had received low doses of conventional agents.

Statistical methods: Values are presented as the mean ± the standard error of the mean and were compared using a 1-way analysis of variance for groups and Dunnett's test to differentiate individual means. A Student t test was used to compare values between 2 samples; results were considered significant at the $p < 0.05$ level.

Results

Acute electrophysiologic data: Twenty-one patients had sustained VT and 19 had nonsustained VT provoked during the control electrophysiologic study. Sustained VT was terminated by pacing in 40% of patients and by electrical cardioversion in 60%. Of the total group of 40 patients tested, 26 (65%) were protected by flecainide and in 14 (35%), VT was inducible despite the drug treatment. The electrophysiologic findings are listed in Table I. Patients were given a mean dose of 1.5 ± 0.1 mg/kg of flecainide, which resulted in a plasma level of 230 ± 20 ng/ml. There was a 12% increase in the PR interval ($p < 0.05$) and a 12% and 22% increase in the refractory periods of the first and second extrastimuli, respectively ($p < 0.01$) for all 40 patients tested. Comparing the percent change in refractory periods while receiving the antiarrhythmic agent to the initial determination for each patient, flecainide caused a significant increase in the refractory period of the first and second extrastimuli for the protected patients (17 ± 2% and 21 ± 3%), in contrast to only a 7 ± 3% and 6 ± 4% increase in the nonprotected patients ($p < 0.05$), despite a higher mean dose (1.9 ± 0.1 nonprotected vs 1.35 ± 0.1 mg/kg protected).

Of the 7 patients who presented with a cardiac arrest, 6 (85%) were protected by flecainide and 4 (57%) by procainamide therapy. Sixty-five percent of the patients with symptomatic VT were protected by flecainide and the same number by procainamide therapy. Forty-eight percent of the patients with asymptomatic VT were protected by flecainide at acute drug testing and 57% by procainamide. The 1 patient who presented with syncope of uncertain cause was protected by treatment with both drugs at PES studies.

The number of stimuli required to induce VT and the presenting arrhythmia are listed in Table II. Among patients with what might be considered the greater risk for electrical instability (cardiac arrest), VT was inducible in most cases by 2 stimuli, whereas the symptomatic VT and asymptomatic VT groups were very similar in their pattern of inducibility. With flecainide therapy, the threshold for inducibility was higher in 5

TABLE II Number of Stimuli Required for Induction of Ventricular Tachycardia (VT)

Extrastimuli	1	2	3	4
Cardiac arrest*	0	4 (57%)	1 (14%)	0
Syncope	0	0	1 (100%)	0
Symptomatic VT	1 (5%)	4 (20%)	8 (40%)	7 (35%)
Asymptomatic VT	1 (8%)	1 (8%)	5 (42%)	5 (42%)

* In 2 additional patients VT was induced with ventricular burst pacing.

TABLE IV Electrocardiographic Changes During Chronic Flecainide Therapy

	Off Drug	1 mo.	3 mo.	6 mo.
Heart rate (beats/min)	72 ± 2	74 ± 3	82 ± 3	79 ± 6
PR interval	171 ± 9	194 ± 7	176 ± 11	192 ± 12
QRS interval	81 ± 3	95 ± 7*	102 ± 10*	100 ± 5*
QT interval	369 ± 8	387 ± 7	382 ± 11	387 ± 10

Significant increase from initial value off drug: * $p < 0.05$.

patients, did not change in 2, and was lower in 6. One patient had a clear arrhythmogenic response to the drug: Spontaneous VT developed during the loading period and required defibrillation. The runs of VT subsided within 6 hours after drug administration was terminated.

Comparison with procainamide: Thirty patients were also tested with procainamide as a reference agent. Procainamide was administered intravenously, 100 mg every 5 minutes to a total dose of 1,000 mg, and if this did not provide protection at PES, an additional 500 mg was administered in a similar manner. Procainamide concentration was 7.8 ± 0.4 μg/ml (8.4 ± 0.3 for the protected and 7.2 ± 0.5 for the nonprotected group). Only patients who did not have a clinical event on procainamide or intolerable side effects were studied with this agent in the laboratory. A comparison of the electrophysiologic data only for patients tested with both drugs is given in Table III. In the group of patients tested with both drugs, 63% of the patients tested with flecainide were protected from VT, compared with 60% protected by procainamide.

Long-term follow-up: Of the 26 patients protected by flecainide during the acute electrophysiologic testing, 21 were discharged from the hospital with flecainide therapy. Five of these 21 patients had presented with a cardiac arrest, 11 with symptomatic VT and 5 with asymptomatic VT. All patients initially received 100 mg twice daily and 18 patients were discharged with this dose. In 2 patients the dosage was increased to 100 mg 3 times daily, and in 1 patient to 200 mg twice daily because of inadequate plasma levels (<200 ng/ml) or because of continued high-grade ventricular ectopy. There was an 85% reduction in ventricular ectopic activity and complete abolition of all VT events at these doses. The patients were followed for a mean of 11 ± 1.5 months. During this period, 2 have died: 1 died suddenly (flecainide level—peak 772 ng/ml and trough 644 ng/ml) and 1 died from a noncardiac cause. One patient had several runs of breakthrough VT at a flecainide dose of 100 mg twice daily, with peak serum concentrations of 990 ng/ml and trough of 679 ng/ml. She was switched to high-dose procainamide treatment and has since died. The patient who died suddenly originally presented with asymptomatic VT on Holter, 9 months after a subendocardial myocardial infarction; the patient who had breakthrough arrhythmias originally had had near-syncope from sustained VT. Two patients have been switched to quinidine treatment by their referring physicians because of unease at continuing an experimental drug, despite continued efficacy. Sixteen patients continue to receive flecainide without problems. Thus, of the patients who continued to receive flecainide treatment, 2 of 19 (11%) have had a breakthrough arrhythmia while receiving chronic therapy, although they were protected during acute testing. None of the patients who presented with a cardiac arrest have had recurrent VT or a repeat arrest.

Long-term electrophysiologic data: The PR, QRS, and QT intervals at acute testing and at 1 month, 3 months and 6 months of follow-up are listed in Table IV. Flecainide had no effect on heart rate or PR or QT intervals; however, it did cause a 24% widening of the QRS complex during long-term therapy ($p < 0.05$). No trend toward further widening was noted during follow-up, and there were no apparent clinical complications from the increased QRS interval. Plasma levels of the group that received chronic therapy were 536 ± 77 at 1 month, 525 ± 95 at 3 months and 704 ± 178 at 6 months of follow-up. Four patients have required a gradual reduction in flecainide dosage over several months because of increases in the serum concentration, QRS widening, heart rate slowing, confusion, and dizziness, from 100 mg twice daily to 50 mg 3 times daily or 50 mg twice daily. Despite the smaller daily dosages, the plasma levels have remained between 500 and 700

TABLE III Comparison of Electrophysiologic Measurements for the Groups Not Receiving Antiarrhythmic Therapy

	HR (beats/min)	PR (ms)	QRS (ms)	QT (ms)	S_2 (ms)	S_3 (ms)
No therapy	76 ± 3	168 ± 5	93 ± 5	387 ± 7	249 ± 5	213 ± 11
Flecainide						
19 protected	73 ± 3	190 ± 7*	93 ± 3	386 ± 7	283 ± 5**	259 ± 5**
11 not protected	74 ± 4	187 ± 8	114 ± 9	415 ± 9*	275 ± 17	283 ± 24
Procainamide						
18 protected	74 ± 2	189 ± 6*	89 ± 3*	398 ± 12	291 ± 6**	258 ± 7**
12 not protected	72 ± 4	189 ± 6*	116 ± 8*	435 ± 13*	300 ± 9**	281 ± 32*

Significant difference compared to patients off therapy: * $p < 0.05$; † $p < 0.01$.

ng/ml. All 4 of these patients clinically have signs of congestive heart failure (New York Heart Association class II), although their mean ejection fraction was 33%.

Adverse reactions: Few adverse reactions have been noted in the patients discharged with flecainide treatment using the lower dosage. One patient has complained of mild neurologic symptoms, primarily dizziness, vague paresthesias and nausea. Two patients had plasma flecainide levels of greater than 1,000 ng/ml before their daily dosage was reduced; both complained of feeling distinctly unwell, with confusion and dizziness. The flecainide levels were 1,081 and 1,099 ng/ml and the symptoms disappeared when the dosage was reduced. One patient had gastrointestinal discomfort with oral flecainide administration.

Serious sinus dysfunction with bradycardia developed in 4 patients predisposed to this problem by evidence of asymptomatic sick sinus syndrome. None of these patients had had significant sinus pauses while receiving previous antiarrhythmic therapy (2 patients receiving procainamide and 2 receiving quinidine) and none had required temporary or permanent pacing. When given flecainide, all 4 required placement of a permanent pacemaker for prolonged sinus pauses (from 2.0 to 3.7 seconds) with nodal or ventricular escape beats developing within 3 days after being started on a dose of flecainide, 100 mg twice daily. After continued observation over the next few days, pauses of longer than 3.5 seconds or paroxysmal atrial tachycardia with 7:1 block and a ventricular response of 31 were noted and a permanent pacemaker was needed in each case. Two other patients had chronic atrial fibrillation but no evidence of "tachy-brady" syndrome; neither of these patients required pacing. None of the other 15 patients with clinically normal sinus node function have demonstrated any instances of sinus or atrioventricular block.

Discussion

Flecainide has been reported to cause a marked reduction in VPC frequency.[3–8] This suppression in VPC frequency is also noted with other class IC drugs such as encainide.[16] These data suggest that flecainide may be a useful new agent for the treatment of VPCs. Less information is known regarding the efficacy of flecainide in patients with life-threatening arrhythmias and in patients undergoing electrophysiologic studies.[10,11]

We studied the effects of flecainide treatment in 40 patients with serious ventricular arrhythmias, all of whom had VT provoked at electrophysiologic testing without antiarrhythmic medication. With an ejection fraction of 45 ± 3% and having only failed 1.9 ± 0.2 drugs before referral, this group of patients would not be considered "drug-resistant," and therefore may be more representative of the usual patient who receives antiarrhythmic therapy for life-threatening arrhythmias. In this group, flecainide protected 65% of the patients. To allow comparison to other centers with a different referral population, we report data on the 30 patients tested with both procainamide and flecainide. Flecainide was as effective as procainamide treatment, 63% vs 60%. In populations with lower ejection fractions or who have failed treatment with more antiarrhythmic drugs, the absolute numbers will be lower, but we believe that flecainide is an effective agent that should be tested.

The correlation between success at acute testing and protection from clinical events in long-term follow-up appears good. In 11 months, 2 patients (11%) had an arrhythmia breakthrough during flecainide therapy, which resulted in 1 (5%) sudden death. This is consistent with results from other PES studies[11] and is consistent with the high risk of this population, which included 7 patients with previous cardiac arrest and 11 with hemodynamically significant, sustained VT. Without a concurrent control group, these numbers are difficult to interpret, but appear to be an improvement over mortality observed with historic controls, especially because none of the patients who had had a cardiac arrest before therapy have died.[17–20]

Flecainide appears to be a well tolerated drug, especially at the reduced doses used in this study. We had only 3 instances of central nervous system and gastrointestinal toxicity in our patients; all of these side effects have been noted by other investigators.[21,22] Four patients had a history of intermittent episodes of atrial fibrillation, flutter or supraventricular tachyarrhythmias and pauses suggestive of sick sinus syndrome. None of these patients had had sinus pauses during previous, ineffective antiarrhythmic therapy (procainamide in 2 patients and quinidine in 2) and none had required temporary or permanent pacing. When given flecainide, all 4 required placement of a permanent pacemaker for prolonged sinus pauses, which occurred within 3 days of oral therapy. Hellestrand et al[23] described sinus node function in 10 patients tested with flecainide during electrophysiologic studies. Although there were no statistically significant increases in the sinus node recovery times in either the patients with normal or abnormal sinus node function, 1 patient had a marked prolongation of her corrected sinus node recovery time, from 3,885 to 18,195 ms. They concluded that flecainide should be used with caution in patients with abnormal sinus node function. Vik-Mo, Ohm and Lund-Johansen[24] studied 11 patients with sinus node dysfunction and found a significant increase in the corrected sinus node recovery time, from 875 ± 181 to 1,727 ± 507 ms ($p < 0.05$). They also advised caution in using flecainide therapy in patients with sick sinus syndrome. Pacemaker thresholds appear to increase by as much as 200% with chronic oral flecainide therapy.[23] This may further increase the risk of patients with a sick sinus who are treated and later require a permanent pacemaker. These considerations should not decrease the utilization of this highly effective agent, but rather caution the prescriber to be observant for the patient who may require pacemaker implantation with flecainide therapy.

Dosage considerations are also important. Toxicity is increased when the level is increased over 1,000 ng/ml. Four patients required a reduction in their maintenance therapy or their plasma level would have gone into the toxic range. Besides the central nervous system and

gastrointestinal symptoms that could be avoided, levels over 1,000 ng may be more likely associated with arrhythmias. Because of a previous report of a case of flecainide toxicity that led to death,[12] we were cautious not to obtain high plasma levels and an associated increase in QRS duration. Flecainide in excessive concentrations may cause a wide complex tachycardia, leading to ventricular fibrillation or asystole unresponsive to defibrillation and pacing.[12] The known elevation in pacing threshold[23] and the probable increase in defibrillation threshold emphasizes the need for moderate plasma levels. Frequent early blood level monitoring during the first month and every 3 months thereafter can be of great help in this regard. Furthermore, evidence from the present study suggests that a subpopulation of patients with clinical symptoms of congestive heart failure may show a rise in flecainide plasma concentrations over time; these patients require more careful monitoring.[25]

Mechanism of action: The current study suggests that flecainide is effective in patients in whom it causes a significant prolongation in myocardial refractoriness as measured by the extrastimulus technique. Although intravenous flecainide therapy causes prolongation in the effective refractory period of the first extrastimulus in all patients tested (12 ± 3%), the change is not directly related to dose. In fact, patients protected by flecainide treatment had a 17 ± 2% increase in the first extrastimulus refractory period with a dose of 1.35 ± 0.1 mg/kg, whereas the nonprotected patients only had a 7 ± 3% increase, but received a higher mean dose of 1.9 ± 0.1 mg/kg. Of all the drugs studied in our laboratory, flecainide most clearly shows this differential prolongation in refractoriness between the patients in whom it was effective and ineffective. However, excessive prolongation of refractoriness could also be arrhythmogenic, as noted both in a previous report of a toxicity in a patient[12] as well as possibly explaining the flecainide toxicity in patients studied by Reid et al.[14]

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Effect of Electrical Activation Site on Left Ventricular Performance in Ventricular Tachycardia Patients with Coronary Heart Disease

JOEL S. RAICHLEN, MD, JONATHAN M. LINKS, PhD, and PHILIP R. REID, MD

Some patients with ventricular tachycardia (VT) remain virtually asymptomatic, whereas others have syncope despite similar VT rates. The role of ventricular activation site on left ventricular (LV) function was examined in 10 patients undergoing electrophysiologic evaluation for recurrent ventricular arrhythmias. Radionuclide ventriculograms were acquired to calculate LV volumes and aortic or LV pressure was measured during right atrial and right ventricular (RV) pacing. RV apical pacing resulted in end-diastolic volumes similar to those achieved with right atrial pacing (171 ± 27 vs 175 ± 19 ml), whereas RV outflow tract pacing showed a trend toward lower volumes (168 ± 32 vs 177 ± 33 ml). Comparison between RV apical and RV outflow tract pacing showed that apical activation resulted in higher end-diastolic volumes (216 ± 26 vs 194 ± 22 ml, p = 0.020), end-systolic volumes (175 ± 25 vs 158 ± 20 ml, p = 0.041), stroke volumes (42 ± 4 vs 36 ± 6 ml, p = 0.046), peak rates of LV ejection (309 ± 57 vs 245 ± 40 ml/s, p = 0.034) and peak rates normalized for differences in end-diastolic volume (1.5 ± 0.3 vs 1.3 ± 0.3; p = 0.047) without a significant increase in peak pressures (131 ± 12 vs 127 ± 14 mm Hg, p >0.30) or ejection fractions (24 ± 5 vs 22 ± 4%, p = 0.187). These changes were accompanied by an increase in LV/RV stroke count ratios during RV apical vs RV outflow tract pacing (1.6 ± 0.2 vs 1.2 ± 0.2, p = 0.030), suggesting the development of mitral regurgitation. Temporal Fourier analysis of the radionuclide ventriculograms showed considerable variation in the LV patterns of emptying from different activation sites. It is hypothesized that the altered activation sequence associated with RV apical pacing disrupts papillary muscle function, inducing mitral regurgitation and, as a consequence, results in higher LV volumes and ejection rates than RV outflow tract activation. These site-dependent differences in LV performance suggest that the location of ventricular activation may be an important determinant of the hemodynamic consequences of sustained ventricular tachyarrhythmias.

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Although ventricular tachycardia (VT) is often associated with severe hypotension, individual patients may present with a broad spectrum of hemodynamic responses to their tachyarrhythmias despite similar VT rates. The mechanisms accounting for the wide range of clinical effects is unknown. Considerable interest has been focused on localizing the specific site of initial activation in VT, but little attention has been directed to the hemodynamic consequences of the altered contraction pattern that results. Investigations of persons with normal hearts or those with valvular or a combination of cardiac diseases have shown no pacing site–dependent differences in left ventricular (LV) hemodynamics,[1–3] while another that focused on patients with coronary disease showed significant variation in cardiac index.[4] Since coronary artery disease is the most common underlying abnormality in patients with sustained ventricular arrhythmias, the origin of ectopic foci may play an important role in the consequences of the rhythm disturbances. Accordingly, we undertook this study to examine patients with coronary disease and recurrent ventricular arrhythmias in order to evaluate the influence of the site of electrical activation on LV function.

From the Division of Cardiology, Department of Medicine and the Division of Nuclear Medicine, Department of Radiology, The Johns Hopkins Hospital, Baltimore, Maryland. This study was supported in part by Training Grant 2-T32-HL-07227 from the National Institutes of Health, Bethesda, Maryland. Manuscript received April 19, 1984; revised manuscript received August 22, 1984, accepted August 23, 1984.

Dr. Raichlen's current address: Joel S. Raichlen, MD, Thomas Jefferson University Hospital Division of Cardiology, Suite #5611, 111 South 11th Street, Philadelphia, Pennsylvania 19107.

Address for reprints: Philip R. Reid, MD, Division of Cardiology, Sinai Hospital of Baltimore, Belvedere at Greenspring Avenue, Baltimore, Maryland 21215.

Methods

Study population: The subjects in this study consisted of 10 men with coronary heart disease undergoing electrophysiologic evaluation for recurrent ventricular tachycardia.

Their average age was 64 ± 3 years (mean ± standard error of the mean). None had clinical evidence of valvular regurgitation.

The protocol was approved by the institution's human investigations committee, and the subjects gave informed consent. The subjects fasted overnight in preparation for their catheterization study. No sedatives or routine medications were administered before the study.

Radionuclide ventriculograms: Red blood cells were labeled in vivo with 20 to 25 mCi of technetium-99m. Electrocardiogram-gated blood pool scans were then acquired during normal sinus rhythm using a mobile scintillation camera interfaced to a dedicated portable computer. The heart was imaged during normal sinus rhythm in the anterior and 40° left anterior oblique projections for 6-minute periods. During pacing, 3-minute images were acquired in the 40° left anterior oblique projection. Technically adequate images were obtained in all but 1 subject.

Pacing protocol: Pacing electrodes were positioned in the right atrium and a right ventricular (RV) site through the femoral vein. Before beginning the clinical electrophysiologic study, the hearts were paced from the right atrium and then simultaneously from the right atrial (RA) and the RV site at a rate of 100 beats/min. Simultaneous atrial and ventricular pacing was used to permit control of the atrium, thus preventing sinus competition and retrograde ventriculoatrial conduction while eliminating the atrial contribution to the end-diastolic volume.

Each sequence began with 1 minute of pacing to allow hemodynamic variables to reach a steady state. Pacing was then continued for an additional 3 minutes, during which arterial or LV pressure was recorded and gated blood pool scans were acquired. The procedure was repeated at each RV site used in the electrophysiologic evaluation, the most common being the RV apex and the RV outflow tract (Table I).

Data analysis: LV time-activity curves from automatically generated regions of interest were used to assess LV volumes by a reliable method which generates highly reproducible volumes.[5–8] End-diastolic volume, end-systolic volume, stroke volume and ejection fraction were determined from the volumes generated using the 16 images making up each cardiac cycle. The time course of the LV volume curve was used to determine the peak rate of LV ejection and the peak rate normalized for end-diastolic volume. Additional regions of interest were manually generated over the right and left ventricles to examine the ratio of LV vs RV stroke counts.[9] Temporal Fourier analysis was performed to visualize the pattern of ventricular emptying.[10] The peak arterial or LV pressure was determined from the equilibrium portion of each pacing sequence. The results found during isorhythmic pacing sequences were compared using analysis of variance for multiple group comparisons and the two-tailed *t* test for assessment of paired data.

Results

The characteristics of the study population are shown in Table I. The gated blood pool scans obtained at rest during normal sinus rhythm showed an average ejection fraction of 35 ± 4% and average end-diastolic volume of 203 ± 23 ml. None had LV/RV stroke count ratios below 1.0, indicating the absence of tricuspid regurgitation at rest.

Similar end-diastolic volumes were found during RA pacing and simultaneous pacing from the right atrium and the RV apex (175 ± 19 vs 171 ± 27 ml), whereas pacing from the right atrium and the RV outflow tract showed a trend toward lower volumes (177 ± 33 vs 168 ± 32 ml) (Fig. 1) (differences not statistically significant). Comparison between pacing from the RV apex vs the RV outflow tract showed higher end-diastolic volumes during RV apical activation (216 ± 26 vs 194 ± 22 ml, p = 0.020) (Fig. 2). RV apical pacing also resulted in higher end-systolic volumes than RV outflow tract pacing (175 ± 25 vs 158 ± 20 ml; p = 0.041). All but 1 patient had a higher ejection fraction during RV apical pacing, though the differences were not statistically significant (24 ± 5 vs 22 ± 4%; p = 0.187). With higher end-diastolic volumes and a trend toward higher ejection fractions, RV apical pacing resulted in higher stroke volumes than pacing from the RV outflow tract (42 ± 4 vs 36 ± 6 ml, p = 0.046). The peak rate of LV ejection was also higher during RV apical pacing (309 ± 57 vs 245 ± 40 ml/s, p = 0.034), as was the peak ejection rate normalized for differences in end-diastolic volume (1.5 ± 0.3 vs 1.3 ± 0.3 end-diastolic volumes/s, p = 0.047) (Fig. 3). Despite the higher ejection rates and larger volumes, there were no differences in the peak pressures generated during RV apical vs RV outflow tract pacing (131 ± 12 vs 127 ± 14 mm Hg; p > 0.30). There were differences, however, in the LV/RV stroke count ratios, with higher values found during RV apical than RV outflow tract pacing (1.6 ± 0.2 vs 1.2 ± 0.2, p = 0.030).

The Fourier phase sequences resulting from the activation sites suggested very different patterns of ventricular emptying. Figure 4, top panel, shows the su-

TABLE I Characteristics of the Patient Population

Subject	Age (yr)	EF* (%)	EDV* (ml)	Sites Paced RA	RV Apex	RV OT	RV IT
1	68	59	69	+		+	+
2	56	51	138	+	+		
3	48	24	237	+	+	+	
4	68	33	210	+	+	+	
5	69	15	286	+	+	+	
6	78	42	145	+	+	+	
7	56	26	232	+	+	+	
8	72	39	171	+	+		
9	53	21	299	+	+	+	
10	68	43	245	+	+		
Mean ± SEM	64 ± 3	35 ± 4	203 ± 23				

* Determined from gated blood pool scans at rest during normal sinus rhythm.

EDV = end-diastolic volume; EF = ejection fraction; IT = inflow tract; OT = outflow tract; RA = right atrium; RV = right ventricular; SEM = standard error of the mean.

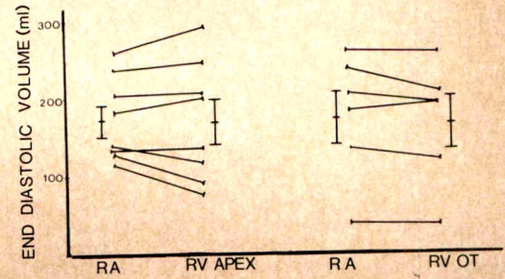

FIGURE 1. End-diastolic volumes calculated from gated blood pool scans during constant rate pacing from the right atrium (RA), right ventricular (RV) apex, and right ventricular outflow tract (OT). **Vertical bars** represent the mean ± 1 standard error of the mean.

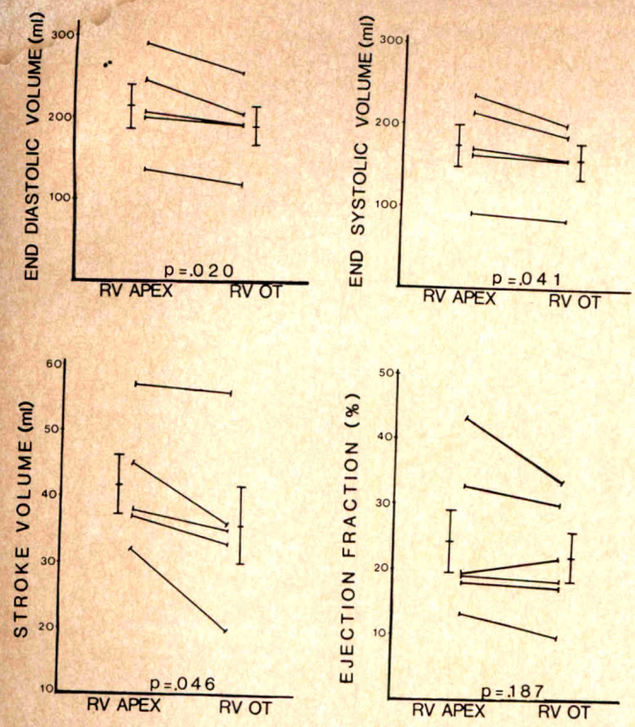

FIGURE 2. Functional variables determined during right ventricular (RV) pacing at a constant rate from the apex vs the outflow tract (OT): comparisons between end-diastolic volume, end-systolic volume, stroke volume and ejection fraction.

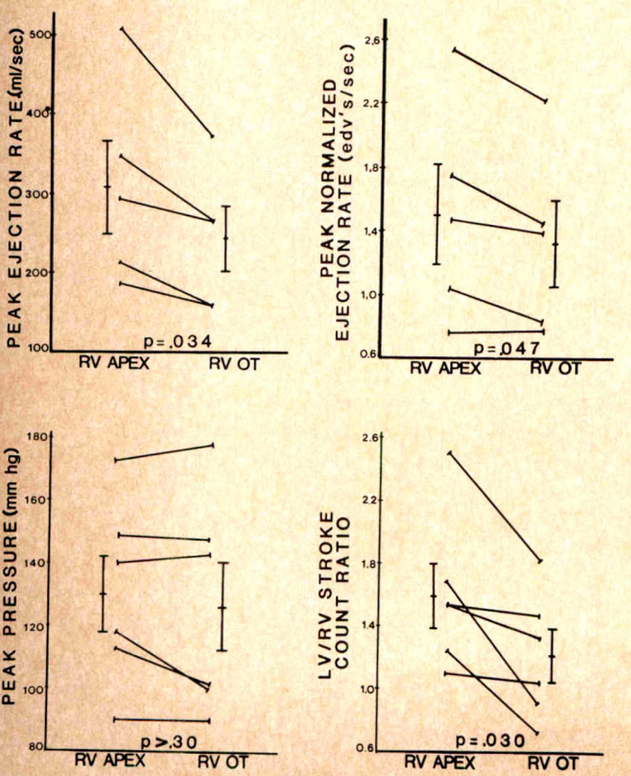

FIGURE 3. Comparisons of peak left ventricular ejection rates, peak rates normalized for end-diastolic volume (edv), peak pressures and the ratios of left vs right ventricular (LV/RV) stroke counts during RV apical vs RV outflow tract (OT) pacing.

praventricular activation sequence in which the mid- to high septum is the initial site of LV emptying in the left anterior oblique projection. Once begun, the remainder of the ventricle empties in rapid succession. Figure 4, middle panel, shows the pattern resulting from RV apical stimulation in the same patient. In this case the inferior apex is the first region of the left ventricle to empty, with the sequence gradually progressing from apex to base. The emptying pattern proceeded at a similar rate during RV outflow tract pacing (Fig. 4, bottom). However, in contrast to RV apical activation, the LV emptying sequence during RV outflow tract stimulation proceeded from base to apex.

Discussion

The importance of the site of ectopic ventricular activation on myocardial function has rarely been demonstrated in man. The 1 study that did so showed higher cardiac indexes during epicardial pacing from the RV apex than the RV outflow tract or the LV apex in open-chest, anesthetized patients undergoing coronary surgery.[4] The current study of endocardial pacing in conscious, unmedicated patients showed consistent results, i.e., that the stroke volumes and peak rates of ejection were higher when activation was initiated from the RV apex than from the RV outflow tract. A higher peak ejection rate normalized for differences in end-diastolic volume suggests better ventricular function,[11,12] whereas a higher stroke volume indicates higher cardiac output. The cause of such site-dependent differences in function has not been previously examined in man.

Simultaneous RA and RV stimulation eliminated the augmentation of LV filling normally provided by atrial contraction. This would be expected to reduce end-diastolic volume relative to RA pacing, particularly in a population with myocardial dysfunction due to ischemic heart disease.[13,14] The comparison between RA and RV apical pacing showed no differences in end-diastolic volume, while RV outflow tract activation showed the expected trend toward reduced volumes. Since there was no significant change in ejection fraction between sites, this increase in end-diastolic volume during RV apical pacing would be expected to result in a higher stroke volume and, as a consequence, a higher rate of ejection as was observed. Although preload conditions may contribute to the increase in ejection rate, normalizing for end-diastolic volume did not eliminate the site-dependent differences in peak rates of ejection.

Despite the higher stroke volumes and peak rates of ejection associated with RV apical pacing, there was no increase in peak pressures. This would be reasonable if a portion of the stroke volume went retrograde across an incompetent mitral valve, reducing the volume of blood ejected into the systemic circulation. The induction of mitral incompetence could not only explain the increase in end-diastolic volume, but also, by providing a low pressure conduit for the regurgitation of blood, could account for the increase in peak rates of ejection and stroke volume. Such an underlying mechanism is supported by the LV/RV stroke count ratios,

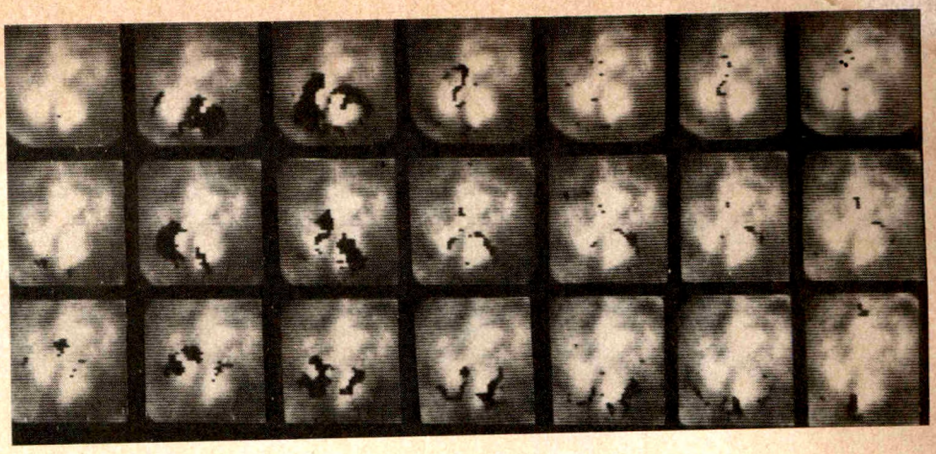

FIGURE 4. Patterns of ventricular emptying during systole displayed as the sequence of pixels (**black dots**) progressing over a composite 40° left anterior oblique gated blood pool image. The images on the left show the areas of the ventricles in which emptying first occurs. Each image in the sequence represents 1/16 of the cardiac cycle. **Top,** supraventricular activation; **middle,** right ventricular apical activation; **bottom,** right ventricular outflow tract activation.

which were significantly higher during RV apical than RV outflow tract pacing.

The likelihood of inducing mitral regurgitation during ventricular activation is enhanced by the loss of atrial contraction. Normally, atrial systole increases ventricular end-diastolic pressure so that the relaxation that follows results in a lower pressure in the atrium than the ventricle. This pressure gradient promotes closure of the atrioventricular valves before the onset of ventricular systole. In the absence of atrial contraction, atrial and ventricular pressures remain equal at end-diastole. With the onset of ventricular contraction, ventricular pressure rapidly rises and a large regurgitation of blood can occur as the atrioventricular valves swing shut from the open position.[15,16] Several studies in animals[15–17] and in man[18] in which atrial pressure tracings were examined have shown evidence of mitral regurgitation during ventricular pacing, whereas others have found no mitral regurgitation during ectopic ventricular activation.[19,20] The results of this study suggest these conflicting findings could relate to the specific locations at which initial ventricular activation occurred. This mechanism is supported by recent observations made during pacing in a canine model.[21]

The mechanism by which certain sites lead to the induction of mitral incompetence may involve the disruption of normal papillary muscle function. In the canine heart, papillary muscle lengthening and shortening has been shown to play an important role in promoting proper coaptation of the mitral valve at end-diastole, in maintaining normal atrioventricular valve function during isovolumic contraction, and in preventing prolapse of the valve leaflets during systolic ejection.[22,23] While the papillary muscles are activated early in systole during normal conduction, the normal contraction sequence can be considerably altered by ectopic electrical excitation.[24] The different contraction patterns suggested by the patterns of emptying during ectopic activation may cause varying delay in papillary muscle contraction relative to the rise of interventricular pressure. In this way, certain stimulation sites may prevent proper apposition of the mitral leaflets, thus precipitating mitral regurgitation. This mechanism may be particularly important in ischemic heart disease, wherein regional contraction abnormalities (particularly at high heart rates) would exacerbate papillary muscle dysfunction.

In this investigation, the study population was characterized by severe myocardial dysfunction and, in particular, by ischemic heart disease. The presence of these abnormalities may have been important in enabling the demonstration of statistically significant, site-dependent functional alterations, despite the small number of patients paced from multiple RV sites. Future investigations should consider the specific myocardial substrate abnormalities that are present when designing studies to evaluate the hemodynamic effects of ectopic activation.

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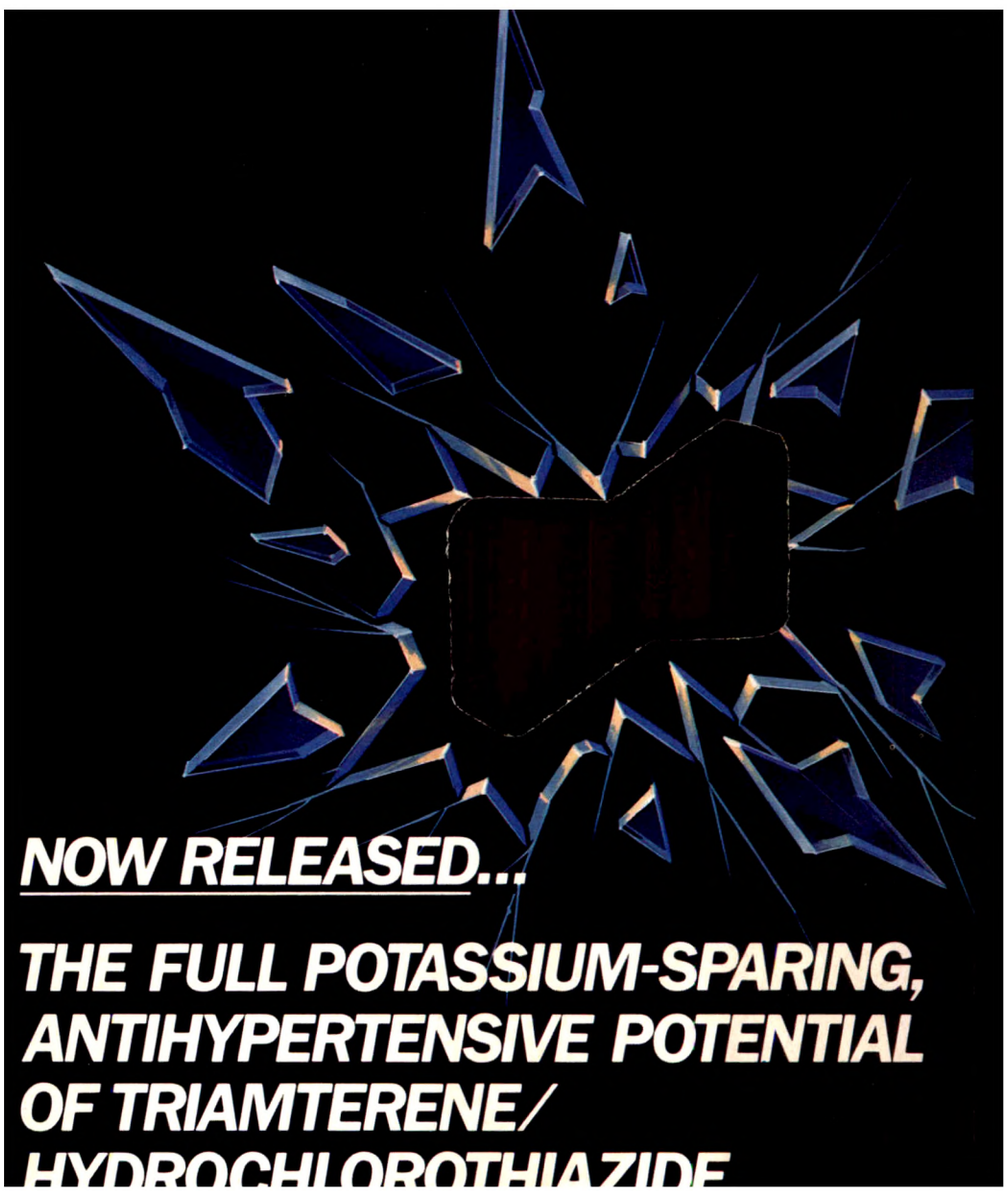
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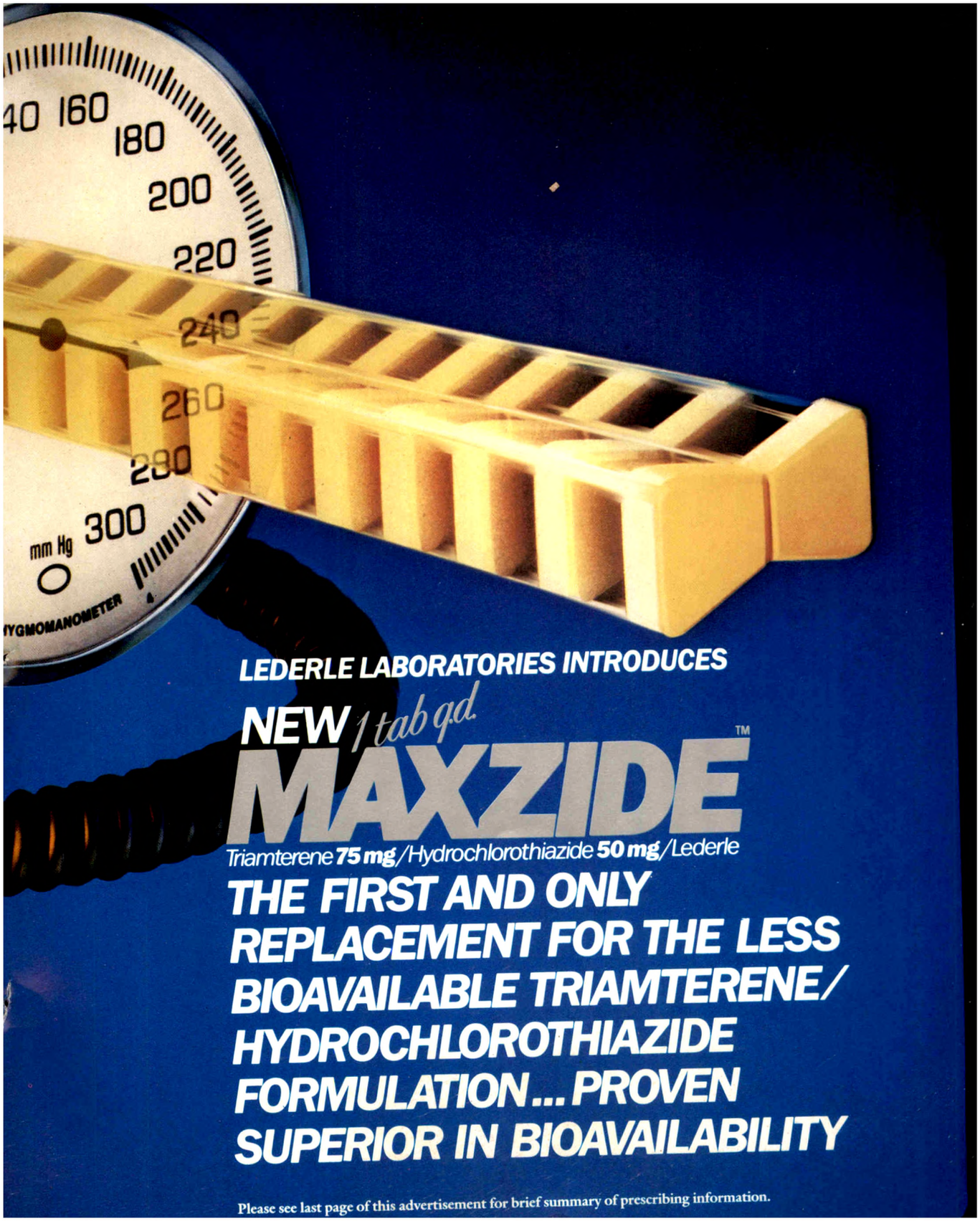

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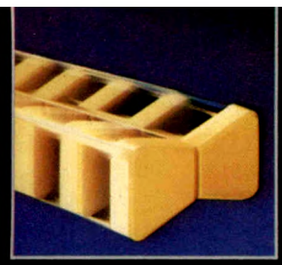

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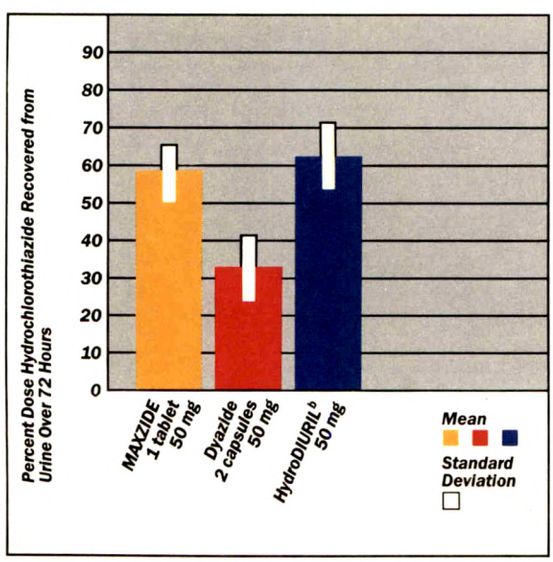

[a]Data from a study of 24 subjects.

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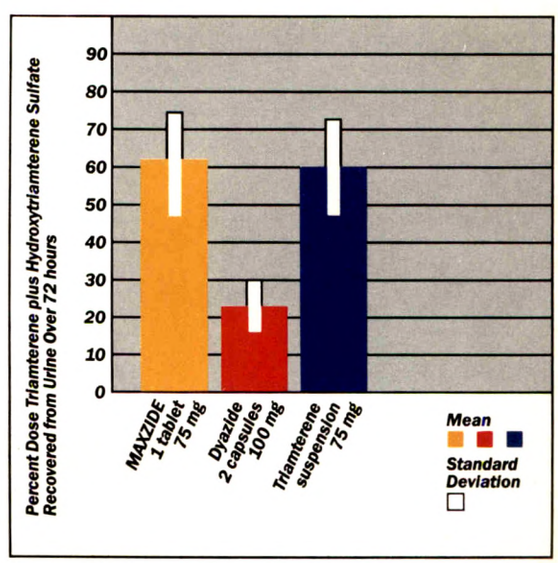

[a]Data from two studies of 24 subjects each.

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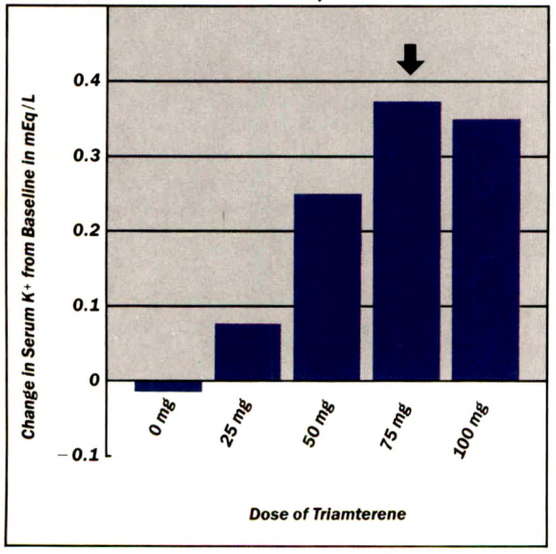
*Ordinarily, triamterene does not entirely reverse the kaliuretic effect of hydrochlorothiazide.



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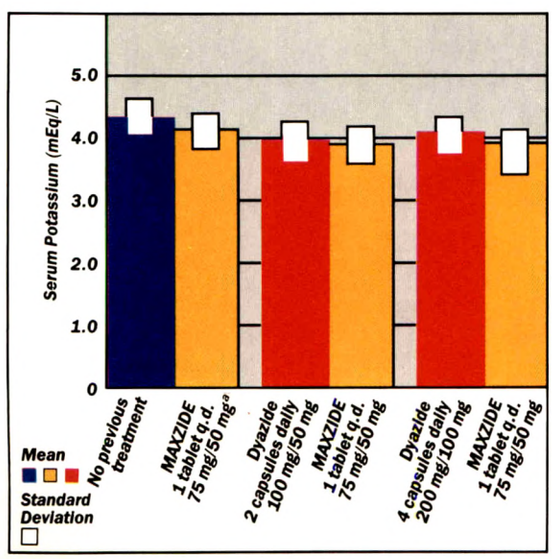

[a]All dose ratios listed as triamterene in mg/hydrochlorothiazide in mg.

[†]Abnormal elevation of serum potassium levels (≥ 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including MAXZIDE. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), or in elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving MAXZIDE, when dosages are changed or with any illness that may influence renal function.

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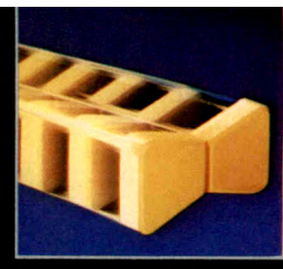

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> *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium conserving agents including MAXZIDE. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), or elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving MAXZIDE, when dosages are changed, or with any illness that may influence renal function.*

If hyperkalemia is suspected, (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock) an electrocardiogram (ECG) should be obtained. Monitor serum potassium levels because mild hyperkalemia may not be associated with ECG changes. If hyperkalemia is present, MAXZIDE should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium level exceeds 6.5 mEq/liter, more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis. The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see CONTRAINDICATIONS). Patients with mild renal functional impairment should not receive this drug without frequent and continued monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide, the pharmacologically active metabolite of triamterene, and the sulfate ester of hydroxytriamterene have been shown to be reduced and the plasma levels increased following MAXZIDE administration to elderly patients and patients with impaired renal function. Hyperkalemia has been reported in diabetic patients with the use of potassium conserving agents even in the absence of apparent renal impairment. Avoid MAXZIDE in diabetic patients. If it is employed, serum electrolytes must be frequently monitored. Metabolic or Respiratory Acidosis: Potassium conserving therapy should also be avoided in severely ill patients in whom respiratory or metabolic acidosis may occur, since acidosis may be associated with rapid elevations in serum potassium levels. If MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg is employed, frequent evaluations of acid/base balance and serum electrolytes are necessary.
PRECAUTIONS: *Electrolyte Imbalance and BUN Increases: Patients receiving MAXZIDE should be carefully monitored for fluid or electrolyte imbalances, i.e., hyponatremia, hypochloremic alkalosis, hypokalemia and hypomagnesemia. Serum and urine electrolyte determinations should be frequently performed and are especially important when the patient is vomiting or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.*

Any chloride deficit during thiazide therapy is generally mild and usually does not require any specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypokalemia may develop with thiazide therapy, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids, ACTH, amphotericin B or after prolonged thiazide therapy. However, hypokalemia of this type is usually prevented by the triamterene component of MAXZIDE.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

MAXZIDE may produce an elevated blood urea nitrogen level (BUN), creatinine level or both. This is probably not the result of renal toxicity but is secondary to a reversible reduction of the glomerular filtration rate or a depletion of the intravascular fluid volume. Periodic BUN and creatinine determinations should be made especially in elderly patients, patients with suspected or confirmed hepatic disease or renal insufficiencies. If azotemia increases, MAXZIDE should be discontinued.

Hepatic Coma: MAXZIDE should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Renal Stones: Triamterene has been reported in renal stones in association with other calculus components. MAXZIDE should be used with caution in patients with histories of renal lithiasis. Folic Acid Deficiency: Triamterene is a weak folic acid antagonist and may contribute to the appearance of megaloblastosis in instances where folic acid stores are decreased. In such patients, periodic blood evaluations are recommended. Hyperuricemia: Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy. Metabolic and Endocrine Effects: The thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

Insulin requirements in diabetic patients may be increased, decreased or unchanged. Latent diabetes mellitus may become manifest during thiazide administration. Hypersensitivity: Sensitivity reactions to thiazides may occur in patients with or without a history of allergy or bronchial asthma.

Possible exacerbation or activation of systemic lupus erythematosus by thiazides has been reported. Drug Interactions: Thiazides may add to or potentiate the action of other antihypertensive drugs.

The thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown to increase responsiveness to tubocurarine.

Lithium, when given with diuretics, reduces renal clearance and increases the risk of lithium toxicity. Refer to the package insert on lithium before use of such concomitant therapy.

Acute renal failure has been reported in a few patients receiving indomethacin and other formulations containing triamterene and hydrochlorothiazide. Caution is therefore advised when administering nonsteroidal anti-inflammatory agents with MAXZIDE.

Drug/Laboratory Test Interactions: Triamterene and quinidine have similar fluorescence spectra; thus MAXZIDE may interfere with the measurement of quinidine.

Pregnancy: Category C: The safe use of MAXZIDE in pregnancy has not been established. Animal reproduction studies have not been conducted with MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg. It is also not known if MAXZIDE can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, pancreatitis, and possibly other adverse reactions which have occurred in the adult. MAXZIDE should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Thiazides appear in breast milk. If the use of MAXZIDE is deemed essential, the patient should stop nursing. Pediatric Use: The safety and effectiveness of MAXZIDE in children has not been established.
ADVERSE REACTIONS: *Side effects observed in association with the use of MAXZIDE include drowsiness and fatigue, insomnia, muscle cramps and weakness, headache, nausea, appetite disturbance, vomiting, diarrhea, constipation, dizziness, decreased sexual performance, shortness of breath and chest pain, dry mouth, depression and anxiety. These adverse reactions are common to other triamterene and hydrochlorothiazide containing products. Other adverse reactions include:*
Hydrochlorothiazide:
Gastrointestinal: anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. Central Nervous System: vertigo, paresthesias, xanthopsia. Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia, megaloblastosis. Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Hypersensitivity: anaphylaxis, purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis. Other: hyperglycemia, glycosuria, hyperuricemia, restlessness, transient blurred vision.
Triamterene:
Hypersensitivity: anaphylaxis, photosensitivity and rash. Other: Triamterene has been reported in renal stones in association with other calculus materials. Triamterene has been associated with blood dyscrasias. Whenever adverse reactions are moderate to severe, therapy should be reduced or withdrawn.
DOSAGE AND ADMINISTRATION: *The recommended dosage of MAXZIDE is one tablet daily with appropriate monitoring of serum potassium levels (see WARNINGS). Patients receiving 50 mg of hydrochlorothiazide who become hypokalemic may be transferred to MAXZIDE directly. In patients requiring 50 mg of hydrochlorothiazide in whom hypokalemia cannot be risked, therapy may be initiated with MAXZIDE. There is no clinical experience with doses exceeding one tablet daily.*

Clinical studies have shown that patients already taking less bioavailable formulations of triamterene and hydrochlorothiazide (totaling 50-100 mg of hydrochlorothiazide and 100-200 mg of triamterene) may be safely changed to one MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg tablet per day; these patients should be monitored clinically and with serum potassium after the transfer.

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Intravenous and Oral Loading Versus Oral Loading Alone with Amiodarone for Chronic Refractory Ventricular Arrhythmias

NICHOLAS Z. KERIN, MD, ROGER D. BLEVINS, PharmD, HOWARD FRUMIN, MD, KATHY FAITEL, RN, BSN, and MELVYN RUBENFIRE, MD

To determine whether combined intravenous (i.v.) and oral loading with amiodarone can shorten its onset of action, a comparative study was conducted. Twenty patients with refractory ventricular arrhythmias were treated with amiodarone. All patients had frequent (≥30/hour) and complex (repetitive) ventricular premature beats on a 48-hour baseline Holter recording. Ten patients (group A) received oral loading alone: 800 mg/day for 7 days, 600 mg/day for 3 days, then a maintenance dose 200 to 400 mg/day. Ten patients (group B) received i.v. and oral loading: 5 mg/kg i.v., and then the same regimen as for group A. Follow-up 24-hour Holter recordings were obtained daily for 7 days, weekly for 1 month, and then monthly. Arrhythmia control was defined as at least a 70% reduction in ventricular premature beats, a 90% or greater reduction in couplets and abolition of ventricular tachycardia. The time to optimal ventricular arrhythmia control was shorter for group B (20 ± 18 vs 105 ± 83 days, $p < 0.05$) and the cumulative amiodarone dose at the time of control was smaller for group B (10 ± 8 vs 48 ± 39 g, $p < 0.05$). No complications were encountered with i.v. amiodarone. Thus, initial loading with i.v. amiodarone can shorten the time to optimal ventricular arrhythmia control and lower the cumulative dose required.

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Amiodarone is a unique antiarrhythmic agent that is effective in the treatment of both atrial and ventricular arrhythmias.[1–3] Early experience with amiodarone has revealed a significant delay in its onset of antiarrhythmic activity, perhaps because of its long half-life.[4] Several investigators have successfully reduced the lag-time by administering large oral loading doses. Nevertheless, in patients with potentially life-threatening arrhythmias, the delay experienced with oral loading regimens is often unacceptable. We compared a combined intravenous (i.v.) and oral loading regimen of amiodarone to an oral loading alone and evaluated the time and cumulative dose required for optimal ventricular arrhythmia control for each approach.

Methods

Patients: The study population included 20 consecutive patients referred to the Arrhythmia Research Clinic at Sinai Hospital of Detroit for management with amiodarone. All patients had a history of chronic ventricular arrhythmias and were intolerant of or refractory to therapeutic doses of conventional antiarrhythmic agents, including quinidine, procainamide, disopyramide and propranolol. In several patients treatment had failed with investigational antiarrhythmic drugs, including aprindine, tocainide, lorcainide and mexiletine. Patients with more than first-degree atrioventricular block without permanent pacing and those with familial long QT syndromes were excluded from this study.

Baseline studies: Antiarrhythmic medications were discontinued for a period of at least 5 half-lives. Digitalis, β-blocking drugs, calcium antagonist drugs and nitrates were permitted when clinically indicated. After washout, a standard 12-lead electrocardiogram (ECG) and a 24- to 48-hour continuous ECG (Holter) were recorded. Holter recordings were stored on magnetic tapes and computer-scanned for the frequency of ventricular premature beats (VPBs), coupled VPBs and ventricular tachycardia (VT), defined as 3 or more consecutive VPBs. Each patient underwent ophthalmologic examinations, routine laboratory studies (including T3, T4 and reverse T3) and chest x-ray.

Study design: The first 10 consecutive patients (group A) received oral amiodarone loading alone. The oral loading regimen consisted of 800 mg/day for 7 days, then 600 mg/day for 3 days, followed by a maintenance dose of 200 to 400 mg/day, depending on clinical judgment. The next 10 patients

From the Section of Cardiovascular Diseases, Department of Medicine, Sinai Hospital of Detroit, and Wayne State University, Detroit, Michigan.
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Address for reprints: Roger D. Blevins, PharmD, Department of Medicine, Sinai Hospital of Detroit, 6767 West Outer Drive, Detroit, Michigan 48235.

(group B) received a combination of i.v. and oral amiodarone loading. This regimen consisted of 5 mg/kg infused over 30 minutes, followed by the group A oral loading regimen. During the infusion, the ECG was monitored continuously by telemetry, and heart rate and blood pressure were determined every 10 minutes. For both groups, 24-hour Holter ECGs were recorded daily for 7 days, then weekly for 1 month, and monthly thereafter. Arrhythmia control was defined as at least a 70% reduction in total VPBs and at least a 90% reduction in coupled VPBs and complete abolition of VT.

Statistical analysis: Between-group differences with respect to baseline and treatment characteristics were analyzed using the unpaired *t* test and significance was inferred at the $p < 0.05$ level.

Results

Patient characteristics: Twenty patients with chronic refractory ventricular arrhythmias were treated with amiodarone. Ten patients (group A) received an oral loading regimen and 10 patients (group B) received a combined i.v. and oral loading regimen. There were no statistically significant differences between group A and group B with respect to age (65 vs 59 years), sex (70% vs 50% male), baseline ventricular arrhythmias (292 vs 265 VPBs/hour, 35 vs 11 couplets/hour and 4 vs 11 VT/24 hours), or number of previous antiarrhythmic drug trials (3.5 vs 3.2 conventional and 1.1 vs 0.2 investigational drug trials per patient).

Control of ventricular arrhythmias: In 7 patients in group A (70%) and in all 10 patients in group B (100%), the ventricular arrhythmias were eventually controlled. The difference was not statistically significant.

The time to arrhythmia control was shorter and the cumulative amiodarone dose at the time of control was smaller for group B than for group A. In group B arrhythmias were controlled 20 ± 18 days (mean ± standard deviation) into therapy with a cumulative amiodarone dose of 10 ± 8 g. In group A arrhythmias were controlled 105 ± 83 days into therapy with a cumulative dose of 48 ± 39 g. Between-group differences in time to control and cumulative dose were significant ($p < 0.05$ and $p < 0.05$, respectively).

Amiodarone was safely initiated and well tolerated in all patients. No patient experienced untoward effects that required discontinuation of treatment during intravenous loading, oral loading or maintenance therapy.

Discussion

Previous studies: The clinical value of amiodarone has been hampered by its delayed onset of antiarrhythmic activity. Several investigators have reported that various oral loading regimens can shorten the lag-time. Rakita and Sobel,[5] in a comparative study with oral amiodarone, reported that the time to complete arrhythmia control was 31 ± 10 days for patients given 200 mg/day and 16 ± 11 days for patients given 1,400 mg/day. Holter ECGs were recorded weekly and arrhythmia control was defined as abolition of recurrent VT and reduction of total VPBs to fewer than 6 per minute.

Other investigators have reported the onset of antiarrhythmic action as 2 to 28 days in uncontrolled studies using various oral loading regimens.[1,6–8] However, some of these studies included patients with supraventricular arrhythmias, and definitions of arrhythmia control varied.

Mostow et al[9] reported control of complex ventricular arrhythmias within 48 hours in 7 patients treated with amiodarone infusions (total dose 1,948 to 4,637 mg) which maintained serum concentrations of 2.0 to 2.5 μg/ml. A more recent study by the same group,[10] using i.v. amiodarone loading (5 mg/kg) followed by a 2-step maintenance infusion guided by pharmacokinetic data (average 2.3 mg/min for 12 hours, then 0.7 mg/min for 36 hours), demonstrated complete suppression of VT in 3 of 7 patients, with a mean VPB suppression of 60%, couplet suppression of 74% and VT suppression of 85%. They concluded that i.v. amiodarone is rapidly effective in control of life-threatening ventricular arrhythmias.

Nademanee et al[11] studied the electrophysiologic effects of amiodarone in 20 patients. Single bolus injections (5 mg/kg) had no significant electrophysiologic effects and the time to significant VPB suppression was not different between 4 patients given 1,600 mg/day orally and 4 patients given a continuous infusion of 50 mg/hour. They concluded that i.v. amiodarone did not shorten the onset of action.

Study design: Combined i.v. and oral loading with amiodarone has not been studied in comparative fashion. In the present comparative study, a relatively low-dose loading and maintenance regimen was chosen in an effort to avoid dose-related side effects (e.g., pulmonary fibrosis), an approach recently advocated by the European Collaborative Group.[12] This low-dose approach, as well as more stringent criteria for optimal control and longer intervals between follow-up visits, make between-study comparisons difficult, but may explain the longer lag-times observed in this study compared to previous studies.

Although the study design was nonrandomized, clinical characteristics were not significantly different between groups. Some of the variability in lag-time observed between groups may be the result of a slightly larger total loading dose for group B or differences in mean pharmacokinetic properties. However, it is unlikely that either of these could fully explain the 5-fold differences observed.

Speculations on the mechanism of intravenous amiodarone: Although significant antiarrhythmic effects have been observed within 24 hours of i.v. amiodarone administration, our data suggest that considerably more time is required for optimal suppression of both frequency and complexity of ventricular arrhythmias. This would indicate that some slow, indirect mechanism, such as accumulation of active metabolite or hormonal effect, is at least partially responsible for its full antiarrhythmic effect. Perhaps the i.v. preparation, having higher systemic availability and more rapid tissue distribution results in a more rapid attainment of indirect effects.

Despite a small patient population and nonrandomized design, we conclude that combined i.v. and oral

loading with amiodarone is well tolerated, shortens the time to optimal arrhythmia control, and reduces the cumulative dose required to achieve arrhythmia control.

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Intravenous Quinidine: Relations Among Concentration, Tachyarrhythmia Suppression and Electrophysiologic Actions with Inducible Sustained Ventricular Tachycardia

HENRY J. DUFF, MD, D. GEORGE WYSE, MD, PhD, DANTE MANYARI, MD, and L. BRENT MITCHELL, MD

A computer simulation was used to devise quinidine sulfate infusions to produce pseudo-steady-state concentrations in the low (8 μM/liter) and high (14 μM/liter) therapeutic ranges, avoiding high peak concentrations. Using this infusion, efficacy and electrophysiologic actions of quinidine sulfate were assessed in 21 patients with sustained inducible ventricular tachycardia (VT) when concentrations were 12.6 ± 11 μM/liter (mean ± standard deviation) and 18 ± 9 μM/liter. Although mean concentrations approximated target levels, there was substantial individual variation. A reciprocal linear relation ($r = 0.8$, $p < 0.01$) was noted between resultant serum concentrations and drug-free ejection fraction (EF). Transient hypotension occurred early in 3 patients, 2 of whom had a normal left ventricular (LV) EF. No hemodynamic compromise was seen in patients with LVEFs of less than 30%. Induced VT was suppressed in 5 patients at low concentrations and in an additional 4 at high concentrations (total 9 of 21, 42%). Concentration-dependent changes in the ventricular effective refractory period of the beat induced by S_3 paralleled antiarrhythmic efficacy. Independent of response or lack of response to intravenous quinidine, 17 patients received gradually increasing oral quinidine dosages adjusted to reproduce plasma levels that had been effective during intravenous administration, or to maximal well-tolerated dosage (if side effects occurred). VT was still inducible during oral treatment in 4 of 5 patients in whom VT had been suppressed during the intravenous infusion. Side effects frequently limited oral dosage to less than that required to reproduce effective concentrations. However, 2 patients did not respond to oral quinidine even when concentrations were equal to those which had been effective during intravenous treatment. In contrast, 11 of 12 patients who did not respond to intravenous quinidine also did not respond to its oral preparation. Response to intravenous quinidine also accurately predicted whether response would ultimately occur to any oral antiarrhythmic agent. In conclusion, acute drug testing to quinidine is safe and efficacious. The discrepancy between antiarrhythmic response to oral and intravenous quinidine is due, at least in part, to poor patient tolerance of large doses of quinidine given orally.

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Although quinidine is effective treatment for some patients with atrial and ventricular tachyarrhythmias, intravenous use of quinidine has been traditionally considered hazardous because of frequent adverse side effects,[1–3] particularly hypotension at peak concentrations. Recent reports have suggested that the use of intravenous quinidine gluconate is not as troublesome as was alleged,[4–6] although hypotension continued to occur frequently in the study of Swerdlow et al.[6] The ability to administer intravenous quinidine safely and achieve a range of therapeutic plasma concentrations would allow a rapid and systematic evaluation of its antiarrhythmic efficacy in individual patients. A computer-simulated infusion was devised to produce pseudo-steady-state concentrations in the low and high therapeutic range with little overshoot. Using this

From the Cardiology Division, Department of Medicine, University of Calgary, and the Foothills General Hospital, Calgary, Alberta, Canada. This study was supported by grants from the Alberta Heritage Foundation for Medical Research, the Alberta Heart Foundation and the Medical Research Council of Canada. Manuscript received March 19, 1984; revised manuscript received and accepted September 6, 1984.

Address for reprints: Henry J. Duff, MD, Department of Medicine, Division of Cardiology, University of Calgary, 3330 Hospital Drive N.W., Calgary, Alberta, Canada T2N 4N1.

infusion protocol, safety, efficacy and electrophysiologic actions of quinidine sulfate were assessed in 21 patients with sustained, inducible ventricular tachycardia (VT).

Methods

Standard infusion: Published pharmacokinetic parameters of quinidine gluconate in normal humans[7–9] were used to design a standard series of infusions producing serum concentrations which gradually increased after an exponential growth pattern to minimize early peaks and troughs. This objective was achieved by giving a series of infusions at decremental rates (Fig. 1). The first series of infusions was designed to produce plasma concentrations in the low therapeutic range (approximately 8 μM/liter). If efficacy was not seen with these low-dose infusions, a second series of infusions was given to produce concentrations in the high therapeutic range (approximately 14 μM/liter). Because volume of distribution of a number of antiarrhythmic drugs, including quinidine,[8] is altered in the presence of congestive heart failure, radionuclide angiograms were performed in a drug-free state so that observed pseudo-steady-state plasma concentrations could be related to baseline ejection fraction (EF).

Protocol: Twenty-one patients with sustained, inducible VT were candidates for this study. These patients were referred for treatment due to: (1) sustained VT; (2) documented nonsustained VT (more than 5 consecutive ventricular ectopic depolarizations at a cycle length of less than 500 ms) that was associated with unmonitored outpatient syncope or that required cardiopulmonary resuscitation; or (3) syncope of obscure origin in patients in whom sustained unimorphic VT could be induced at electrophysiologic study. Sustained VT was defined as consecutive ventricular premature complexes at a cycle length of less than 500 ms lasting longer than 30 seconds, or producing hemodynamic compromise requiring termination of the tachyarrhythmia within 30 seconds.

Each patient gave written, informed consent. After withdrawal of all antiarrhythmic medications (for at least 4 half-lives), programmed electrical stimulation studies were done in a drug-free state. The standard quinidine sulfate infusion was then administered and blood pressure, pulse and clinical status were evaluated every 5 minutes throughout the infusion. Programmed electrical stimulation studies during the first series of infusions were not begun until the infusions had been under way for at least 40 minutes. Blood samples for quinidine assay were obtained just before and after electrophysiologic measurements. When VT induction was not suppressed with the first series of infusions, the higher dose infusion protocol was administered and electrophysiologic studies were repeated no sooner than 30 minutes after beginning the second series of infusions.

Independent of response to intravenous quinidine, consenting patients subsequently received gradually increasing oral dosages of quinidine. The dosage was adjusted to reproduce the serum levels that had been effective during the intravenous quinidine electrophysiologic study or to the maximal tolerated oral dose, whichever was lower. Electrophysiologic testing was then repeated on oral quinidine therapy.

Electrophysiologic studies: The ventricular origin of the patient's arrhythmia was confirmed by His bundle recordings. Programmed electrical stimulation techniques used in the study included introduction of single, double and, if necessary, triple extrastimuli (3 mA or twice diastolic threshold, whichever was greater, and a 2-ms pulse width) at ventricular drive cycle lengths of 600, 500 and 400 ms with the electrode catheter at the apex of the right ventricle.[10] Ventricular burst pacing (4 to 12 beats at cycle lengths of 300 to 240 ms) was subsequently used if VT was not induced by the extrastimulus

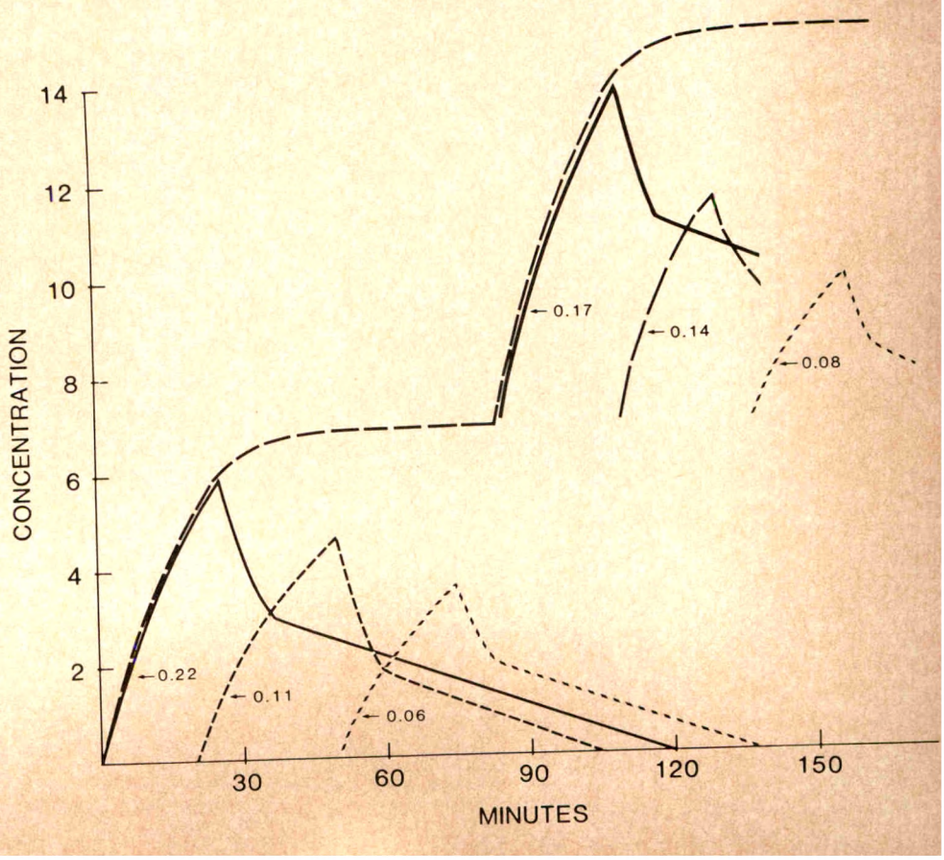

FIGURE 1. A decremental series of infusions produce concentrations that increase in a slow exponential pattern. Low therapeutic plasma concentrations are produced by infusion rates (μg/kg/min, each for 25 minutes) of 0.22, 0.11, 0.06 and higher concentrations by rates of 0.17, 0.14, 0.08.

technique. During the drug-free study the endpoint of programmed electrical stimulation was induction of VT on at least 2 occasions with at least 1 of these being sustained (defined above). During subsequent quinidine studies, the ability to induce at least 5 consecutive ventricular ectopic depolarizations at a cycle length of less than 500 ms was considered to be drug failure.

Concentration-dependent change in other electrophysiologic parameters were also evaluated. Surface electrocardiographic leads I, aVF and V_1 were recorded at baseline and during quinidine treatments, and the PR, QRS, QT and RR intervals were measured. Rate-corrected QT (QTc) was calculated from the formula $QTc = QT/\sqrt{RR}$. Ventricular effective refractory periods (VERPs) of the beats induced by the first and second extrastimuli (S_2, S_3) were also measured using the extrastimulus technique and conventional definitions. Concentration-dependent changes in rate and morphologic pattern of the induced VT were also assessed.

Analytical: Samples were assayed, using an enzymatic immunoassay (EMIT®) method. The therapeutic range for quinidine has been reported to be 7 to 14 μM/liter. Little cross-reactivity to quinidine's major metabolite has been found using this assay.[11,12]

Statistics: One-way analysis of variance was used to assess the significance of changes in electrophysiologic measurements during the quinidine infusions. Chi-square analysis was used for discrete data. The null hypothesis was rejected at the $p < 0.05$ level. Continuous data are presented as mean ± standard deviation.

Results

Patients: Four of the 21 patients had 1 or more episodes of ventricular fibrillation, 9 had spontaneous sustained VT, 5 had nonsustained VT and recurrent outpatient syncopal episodes and 3 were evaluated for syncope of obscure origin. Six of the 21 patients had required 1 or more transthoracic cardioversions for VT and 4 of the patients had required cardiopulmonary resuscitation out of hospital. Seventeen of the patients had ischemic heart disease with a global EF of 42 ± 10%.

Quinidine infusion: The first series of quinidine infusions achieved pseudo-steady-state concentrations of 12.6 ± 11 μM/liter while the second series of infusions produced serum concentrations of 18 ± 9 μM/liter. Mean observed plasma levels were somewhat in excess of the target concentration (7 and 14 μM/liter), and there was substantial interindividual variation. Figure 2 shows a reciprocal linear relation between the drug-free EF and the observed plasma concentrations at electrophysiologic testing ($r = 0.8$, $p < 0.01$). Symptomatic hypotension was seen in 3 patients during the quinidine infusion. Hypotension was promptly corrected by administration of saline solution and did not require the termination of the infusion in any patient. There was no relation between likelihood of developing hypotension and clinical characteristics of the patients or observed serum concentration. Two of the 3 patients in whom hypotension developed had normal left ventricular EF. None of the 6 patients with EFs of less than 30% who were given the standard quinidine infusions had adverse effects.

Concentration-dependent antiarrhythmic and electrophysiologic changes: The antiarrhythmic activity of quinidine sulfate (as assessed by its ability to preclude induction of VT) increased with increasing serum concentrations (Fig. 3). Forty-three percent of the patients responded to intravenous quinidine, and little additional benefit was observed with serum concentrations in excess of 18 μM/liter. Induction of VT with a stimulation protocol which was less aggressive than that required at baseline occurred in 7 patients during the quinidine infusions. VT was easier to induce

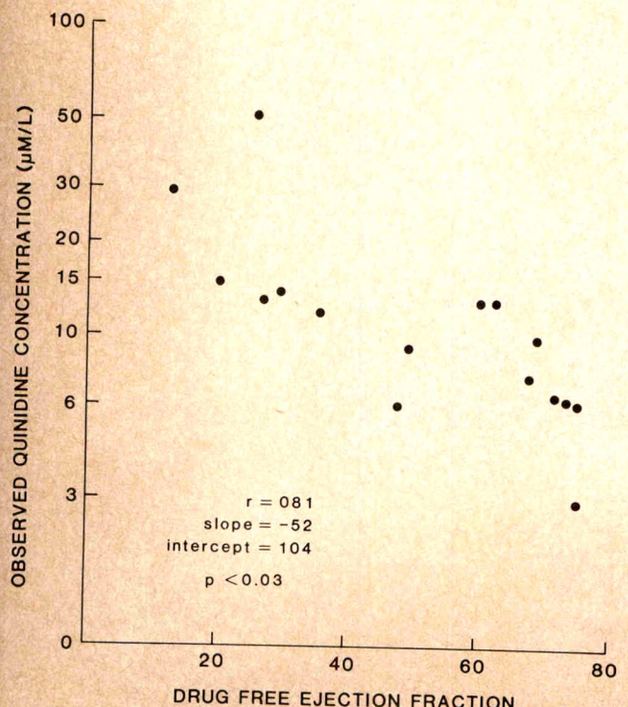

FIGURE 2. A reciprocal relation between plasma concentrations produced and the drug-free ejection fraction.

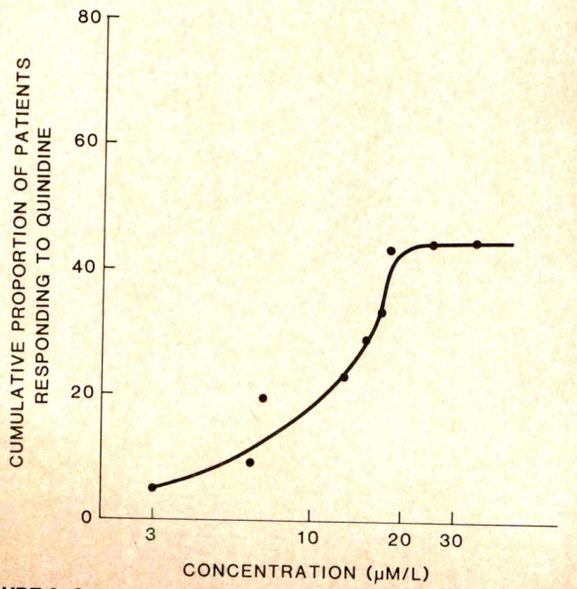

FIGURE 3. Cumulative proportion of patients responding to quinidine with suppression of induced ventricular tachycardia relative to plasma concentration.

TABLE I Inducibility (I) or Noninducibility (NI) of Tachycardia with Intravenous and Oral Quinidine

		Inducibility with Intravenous Quinidine	
		NI	I
Inducibility with oral quinidine	NI	1	1
	I	4	11

Difference not significant (χ^2).

in 4 of the 7 patients at low concentrations, while high-dose quinidine enhanced VT induction in 3 patients. Of interest, 2 of 4 patients in whom VT was easier to induce after low-dose quinidine infusion responded to the larger dose infusion with suppression of inducibility. There was no simple relation between extent of QTc prolongation or VERP change and ease of inducibility. While inducibility of VT was occasionally enhanced by quinidine, paradoxical acceleration of VT rate was not seen. Figure 4 illustrates concentration-dependent changes in electrophysiologic measurements. The VERP of S_2 was increased only to a small degree in these patients and there was little increase in this measurement at concentrations beyond 7 μM/liter. However, the VERP of the beat induced by S_3 progressively increased throughout the concentration range tested and paralleled antiarrhythmic efficacy. The relation between quinidine concentration and change in QRS was linear ($r = 0.62$, $p < 0.05$). A plateau in the concentration-dependent increase in QTc interval occurred at approximately 14 μM/liter. Although the cycle length of induced VT was slowed by quinidine (245 ± 53 ms at baseline; 313 ± 80 ms with low-dose quinidine, and 364 ± 62 with high-dose quinidine) the extent of its slowing did not correlate with serum concentration.

Response to intravenous quinidine as a predictor of response to oral treatment: Independent of the response to intravenous quinidine, 17 consenting patients received gradually increasing oral dosages of quinidine and electrophysiologic studies were repeated. Table I illustrates the relation between inducibility during intravenous quinidine treatment to inducibility during its oral administration. Four of 5 patients who responded to intravenous quinidine did not respond during oral treatment. In 2 of these 4 patients the oral quinidine dose was limited by side effects and the effective concentrations achieved with intravenous quinidine could not be reached. However, VT continued to be inducible during oral therapy in 2 patients who had equal plasma levels during intravenous and oral treatments (Table II). In contrast, the absence of antiarrhythmic response to intravenous quinidine accurately predicted a lack of response to oral quinidine in 11 of 12 patients.

We also assessed whether the antiarrhythmic response to intravenous quinidine would predict eventual response to any oral antiarrhythmic therapy (Tables II and III). Eight of 9 patients who responded to intravenous quinidine finally responded to oral antiarrhythmic medication (Table II). Nine of 12 patients who did not have an adequate antiarrhythmic response to intravenous quinidine did not respond to any oral medication.

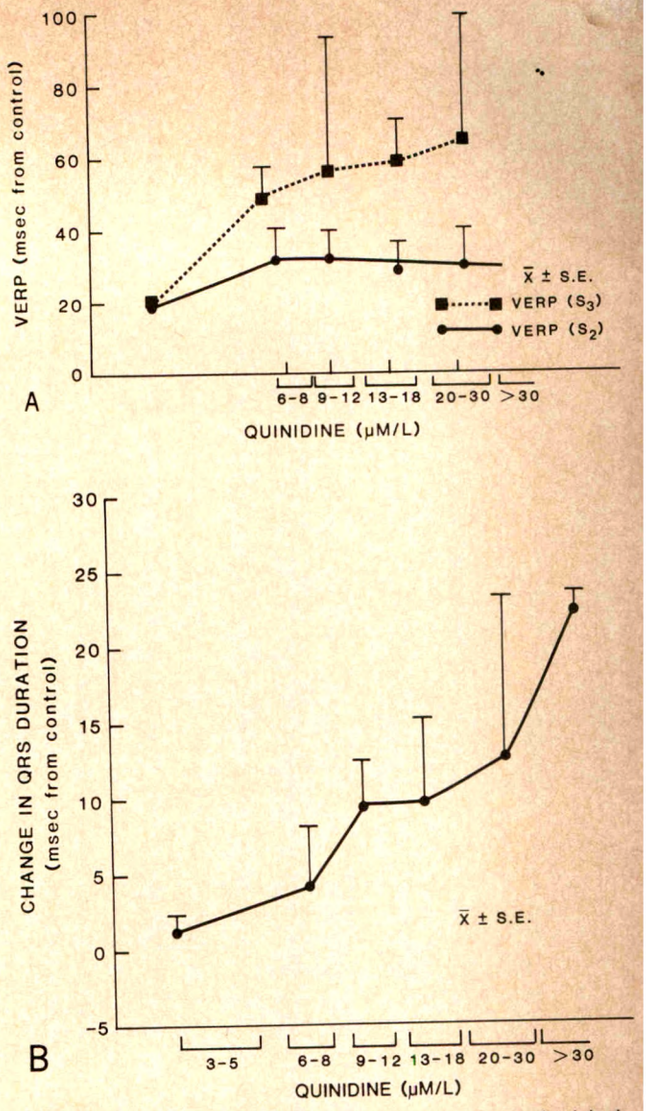

FIGURE 4. Concentration-dependent change in electrophysiologic measurements. **A,** ventricular effective refractory period (VERP) of S_2 and S_3. **B,** QRS duration. S.E. = standard error.

Discussion

Acute electrophysiologic effects of intravenous quinidine have been previously investigated after stopping a rapid infusion of quinidine.[6,13,14] However, concentration-response relations measured during the rapid distribution phase may not be reliable.[15] Furthermore, in previous studies no attempt was made to systematically evaluate antiarrhythmic efficacy over the entire therapeutic range.[6] The rapid infusion technique also increases the likelihood of side effects by producing early high peak levels. Symptomatic hypotension occurred frequently in the study of Swerdlow et al,[6] but it was infrequently seen in the present study. Rapid evaluation of efficacy and pharmacologic actions of intravenous antiarrhythmic agents can be improved when infusions produce pseudo-steady-state serum

TABLE II Individual Patient Responses to Programmed Electrical Stimulation in Relation to Serum Concentration and to Medications Given

	Intravenous Quinidine		Oral Quinidine		Discharge Medications		
Pt	Conc.*	PES	Conc.	PES	Meds	Conc.*	Induc.
1	3	NI	6	NI	Quinidine	6	NI
2	NA	I	9	NI	Quinidine	9	NI
3	14	NI	9	I†	Amiodarone	1	I
4	16	NI	15	I†	Quinidine, propranolol	7 160	NI
5	18	NI	12	I†	Sotalol	2.4	NI
6	13	NI	13	I†	Quinidine, tocainide	9 6	NI
7	6	I	9	I	Sotalol	3.0	I+
8	21	I	11	I	Quinidine, mexiletine	8 0.7	NI
9	26	I	16	I	Amiodarone	1.3	I
10	26	I	NA	I	Amiodarone	NA	I
11	5	I	5	I	Disopyramide	NA	I+
12	29	I	14	I	Amiodarone	NA	I
13	6	I	NA	I	Surgery		I
14	14	I	NA	I	Amiodarone	0.8	I
15	19	I	10	I	Amiodarone	1.1	I
16	53	I	12	I	Amiodarone	2.1	I
17	9	I	NA	NA	Mexiletine	0.7	NI
18	8	NI	NA	NA	Propranolol	39	NI
19	NA	NI	7.4	I	Mexiletine, quinidine	0.8 7.5	NI
20	6	NI	NA	NA	Quinidine, verapamil	NA	NI
21	7	NI	NA	NA	Propranolol	67	NI

* Concentration; the units for each medication are: quinidine, μM/liter; amiodarone, μg/ml; propranolol, ng/ml; sotalol, μg/ml; tocainide μg/ml; disopyramide, μM/liter; mexiletine, μg/ml.
† Patients in whom discordant results were noted between intravenous and oral quinidine.
I = inducible; I^+ = inducible, but optimal treatment; NA = not available; NI = not inducible; PES = programmed electrical stimulation.

concentrations which explore concentration response relations over the entire therapeutic range without side effects.

The quinidine infusion devised for this study did achieve a range of therapeutic concentrations; however, other problems of acute drug testing limit its overall value. Antiarrhythmic effects seen during the acute drug infusion did not predict the response with oral quinidine treatment. Such discrepancies may relate to several factors, including: (1) side effects during chronic oral therapy, which limit dosage increments so that effective concentrations seen with the intravenous quinidine are not reached; (2) a difference in the relation between tissue levels and plasma levels when these are measured under pseudo-steady-state and steady-state conditions; and (3) the presence of active metabolites, which may contribute to pharmacologic actions and side effects. The relative inefficacy of oral quinidine in this study was primarily a result of side effects that limited our ability to reproduce effective plasma concentrations during the infusion. Side effects seen with oral quinidine treatment may reflect local gastrointestinal irritation. Chou[16] evaluated the relation between plasma concentrations and ventricular tissue concentrations of quinidine during a constant infusion in dogs. In that study, there was little discrepancy between intravenous and myocardial concentrations after 90 minutes, suggesting that there is little difference in tissue levels under pseudo-steady-state and steady-state conditions. Two patients did not respond to oral quinidine, even though their plasma levels reproduced concentrations that had been effective during intravenous quinidine therapy. Hypothetically, active metabolites of quinidine could accumulate during long-term oral therapy and as the metabolites are electrophysiologically active[17,18] they could alter antiarrhythmic efficacy.

The infusions designed for this study allowed an evaluation of concentration-related changes in electrophysiologic parameters and their relation to antiarrhythmic activity. No single electrophysiologic change or combination thereof clearly discriminated between patients who would or would not respond to quinidine. However, we noted that change in the VERP of the beat induced by S_3 had a concentration-response relation that paralleled antiarrhythmic activity. Although parallel concentration-response curves do not indicate a cause and effect relation, such observations do suggest potentially fruitful areas of future research. Few other studies in man have systematically evaluated the concentration-response relations of electrophysiologic changes with quinidine. The present data, like previous data from human studies by Heissenbuttel and Bigger,[19] show concentration-dependent changes in QRS duration, QTc interval. Unlike Heissenbuttel's study[19] we evaluated change in VERP (S_2) and observed that its increase occurs at low plasma concentrations (7 μM/liter) with little increase in this measurement at higher concentration. The QTc interval however progressively prolonged and only then plateaued at approximately 12 μM/liter, while QRS increases linearly with concentration. Varying concentration-response relations suggest that quinidine may mediate its elec-

TABLE III Inducibility (I) or Noninducibility (NI) of Tachycardia with Quinidine Compared with Any Oral Antiarrhythmic Agent

		Inducibility with I.V. Quinidine	
		NI	I
Inducibility with any oral antiarrhythmic	NI	8	3
	I	1	9

$p < 0.01$ (χ^2).

trophysiologic actions at a number of different active sites. These results are in keeping with in vitro data[20] that suggests that quinidine's effects on various phases of the action potential are mediated at a number of active sites.

The results obtained with intravenous quinidine in this study are similar to those seen with procainamide. As with procainamide,[21,22] high concentrations of quinidine achieved control of ventricular arrhythmias resistant to more conventional concentrations and acute toxicity at high concentrations was not a major problem.[22,23] Despite the limitation of use of acute intravenous quinidine testing to predictive response to oral quinidine, such testing may be of value in predicting eventual response to any oral antiarrhythmic agent. A similar predictive value[22,23] has been seen relating antiarrhythmic response to procainamide and response to any oral antiarrhythmic agent. Differences are also apparent between quinidine and procainamide. In this study, oral quinidine therapy was not well tolerated, unlike results reported with high-dose oral procainamide.

This infusion was designed from pharmacokinetic parameters derived from administration of intravenous quinidine gluconate. The administered dosage was then adjusted to reflect the relative proportion of the quinidine sulfate molecule, which is base (rather than salt). Theoretically, if the present quinidine infusion were modified so that quinidine gluconate was to be given, the serial intravenous rates would be increased by a factor of 1.34.

In conclusion, an infusion protocol for the administration of quinidine sulfate was devised that permits a rapid and safe assessment of antiarrhythmic efficacy at both low and high therapeutic concentrations in man. Response to intravenous quinidine predicts the likelihood of a response to any oral antiarrhythmic agent. However, this infusion has a major limitation relating to a discrepancy between tolerance to intravenous and oral medication.

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Effect of the Calcium Antagonist Diltiazem on Atrioventricular Conduction in Chronic Atrial Fibrillation

KARL THEISEN, MD, MATHIAS HAUFE, MD, JOCHEN PETERS, FRANZ THEISEN, MD, and HANS JAHRMÄRKER, MD

The effect of oral diltiazem treatment on the mean ventricular rate was studied in 10 patients with stable atrial fibrillation (AF). The profile of mean ventricular rate was analyzed by means of 24-hour electrocardiographic recordings. Both single-dose (120 mg) and maintenance therapy (80 mg 3 times daily) reduced the mean ventricular rate significantly. After the single dose, the effect set in after 120 ± 40 minutes (mean ± standard deviation) and persisted for 347 ± 84 minutes. Histograms of RR intervals were plotted and their changes after diltiazem therapy were also analyzed. The shortest and longest atrioventricular (AV) conduction times were defined as 5% and 95% values of the cumulative frequency curve, respectively. There were 2 distinct types of the RR-interval histographic changes: In 50% of the patients, the longest and shortest RR intervals prolonged proportionately; in the other 50%, the longest intervals increased disproportionately. Results indicate that oral diltiazem treatment can significantly decrease the mean ventricular rate in patients with AF by influencing the concealed conduction in the AV node. The changes of the RR-interval histograms suggest that in 50% of the patients, the increase of the concealed conduction was probably caused primarily by the increase of AF rate, and in 50% both increased AF rate and prolonged refractory period in the AV node contributed to the increase of concealed conduction.

(Am J Cardiol 1985; 55:98–102)

Diltiazem is a slow channel blocking drug.[1] In contrast to the calcium antagonist nifedipine, diltiazem has marked antiarrhythmic effects, similar to those of verapamil.[2–4] In clinical studies, verapamil[5] and diltiazem[6] reversed supraventricular tachycardias. In cases of atrial fibrillation (AF), intravenous[5,7] and oral[8] administration of verapamil, as well as intravenous diltiazem,[9] reduced the mean ventricular rate. The present study assesses the oral effectiveness of diltiazem on the basis of ventricular rate reduction in patients with stable AF. The extent of ventricular rate depression, onset and duration of action, and indications of the mechanism of action were studied.

Methods

Patients: The test group included 10 patients (8 women, 2 men), aged 39 to 81 years. All patients had had stable AF over an extended time. Clinical diagnoses of the patients are shown in Table I. Eight of the 10 patients were taking digitalis maintenance therapy with effective levels in the standard range. None of the patients were treated with other drugs that act on the atrioventricular (AV) node or with other antiarrhythmic agents. All patients were in a clinically stable condition and had given informed consent.

Protocol: Each patient received a single oral dose (120 mg) of diltiazem, and 10 hours later maintenance therapy was initiated (90 mg 3 times daily), and was continued for at least 4 days.

Twenty-four hour electrocardiograms (ECGs) were recorded (Reynolds Pathfinder II system) before treatment (control phase), at the beginning of treatment, and after 3 days of medication. The second 24-hour ECG contained the response of the patients after the single 120-mg dose of diltiazem and at the beginning of the maintenance therapy (90 mg 3 times daily), initiated 10 hours later. The third 24-hour ECG showed the steady-state response of the patients receiving maintenance therapy. From the 24-hour ECGs, the mean ventricular rate was plotted (Fig. 1) and plotting RR-interval histograms for any desired period was also possible (Fig. 2). The onset of action, defined as the point at which 50% of the maximal rate of depression is reached, and the cessation of action, defined as the point at which the 50% maximal rate depression is no longer maintained, were determined in the acute test after the administration of 120 mg of diltiazem (Fig. 1). In the comparison of the control phase and the maintenance phase with 90 mg 3 times daily, both the absolute values of the RR intervals and the mean ventricular rates were used. The 5% and 95% values of the cumulative frequency curves of the RR intervals were defined as the shortest and longest

From the Medizinische Klinik, Innenstadt, Universität München, München Federal Republic of Germany. Manuscript received May 25, 1984; revised manuscript received September 6, 1984, accepted September 10, 1984.

Address for reprints: Prof. Karl Theisen, Medizinische Klinik Innenstadt, Universität München, Ziemssenstr. 1, D-8000 München 2, Federal Republic of Germany.

TABLE I Clinical Data

Pt	Age (yr) & Sex	Diagnosis	Digitalis
1	55F	MR, MS	+
2	56M	AS (AVR)	+
3	67F	MR, MS	0
4	81F	CAD	+
5	39F	MR (MVR)	+
6	54F	AS, MR MS (AVR)	+
7	55M	SH	+
8	57F	MR	+
9	54F	MS	+
10	59F	MR	+

AS = aortic stenosis; AVR = aortic valve replacement; CAD = coronary artery disease; MR = mitral regurgitation; MS = mitral stenosis; SH = systemic hypertension.

AV conduction times, respectively. These values are referred to as fifth and ninety-fifth percentiles in this report. Short RR intervals (represented by the fifth percentile) were taken as measure of the AV refractory period. Prolongation of the long RR intervals (represented by the ninety-fifth percentile) were taken as a measure of the increase in concealed conduction (Fig. 2). The changes of the fifth and ninety-fifth percentile values of the RR-interval histograms were also compared in the control and maintenance phases. (Table II, Fig. 3). Blood levels of diltiazem have been determined in 8 of the 10 patients 90 minutes after oral administration of 120 mg of diltiazem (Table III). Throughout the acute test blood pressure was checked at regular intervals of 1 to 2 hours. Routine clinical examinations and clinical chemistry tests were performed before the investigations.

Results

Ventricular rate reduction in the acute test after 120 mg of diltiazem: After oral administration of 120 mg of diltiazem, a significant ($p < 0.001$) reduction in the mean ventricular rate was achieved in all patients (Table III). The mean (± standard error of the mean) reduction in ventricular rate was 30 ± 5%. The onset of action occurred after 120 ± 40 minutes (range 60 to 180). The duration of action was 347 ± 84 minutes (range 220 to 520). The duration of action was not determined for patient 7 because of technical difficulties. Plasma levels of diltiazem between 17 and 75 ng/ml were found in 7 patients. In 2 patients these values could not be determined. In patient 9, a plasma level of 2 ng/ml was measured.

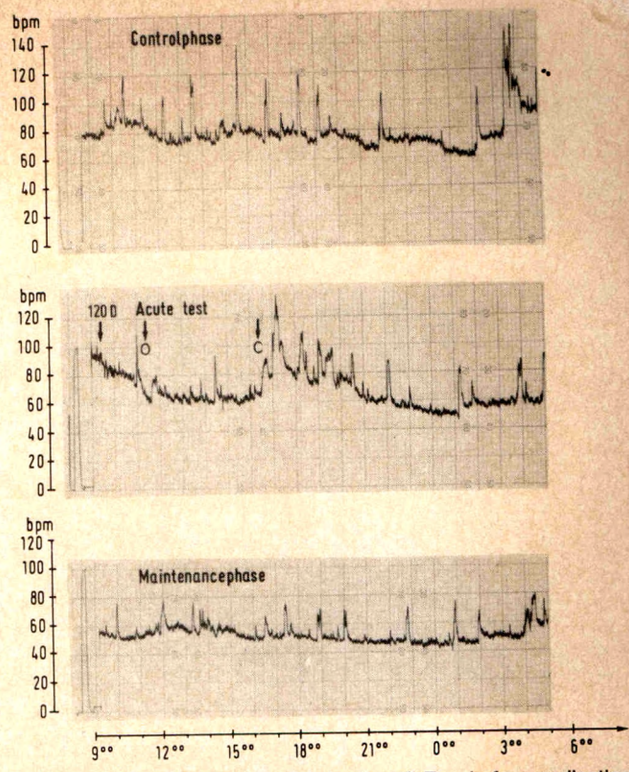

FIGURE 1. Mean ventricular rate of patient 6. **Top,** before medication (control phase). **Middle,** acute effect of diltiazem. A dose of 120 mg was given orally (**arrow**). After onset of action (O, defined as the point when 50% of the maximal rate depression has been reached), the mean ventricular rate remains less than control value for several hours. After cessation of action (C, defined as the point when the 50% maximal rate depression is no longer maintained), the curve returns to the premedication range. After maintenance therapy (90 mg 3 times daily) has been initiated (at 18 hours), the curve drops again. **Bottom,** after 3 days of maintenance therapy, the maintenance phase values remained consistently below the control level. Peaks with relatively rapid heart rate also fell below control values.

Ventricular rate reduction after oral maintenance therapy: The mean ventricular rate was reduced significantly ($p < 0.001$), in patient 4 by 5% and by 11 to 34% in the rest of the patients. The absolute number of

TABLE II Changes in the Shortest (Fifth Percentile) and Longest (Ninety-Fifth Percentile) RR Intervals After Maintenance Therapy with Diltiazem (90 mg 3 Times Daily)

	5th Percentile			95th Percentile		
Pt	Before (ms)	After (ms)	Change (%)	Before (ms)	After (ms)	Change (%)
1	500	750	50	1,050	1,500	43
2	450	500	11	950	1,150	21
3	450	500	11	950	1,150	21
4	500	500	0	1,200	1,350	13
5	400	500	25	900	1,150	28
6	450	700	56	1,050	1,600	52
7	350	500	43	950	1,300	44
8	600	700	17	950	1,350	42
9	450	600	33	1,200	1,600	33
10	550	650	18	1,250	1,750	40

In patients 2, 3, 4, 8 and 10 the longest RR intervals increased more than the shortest.

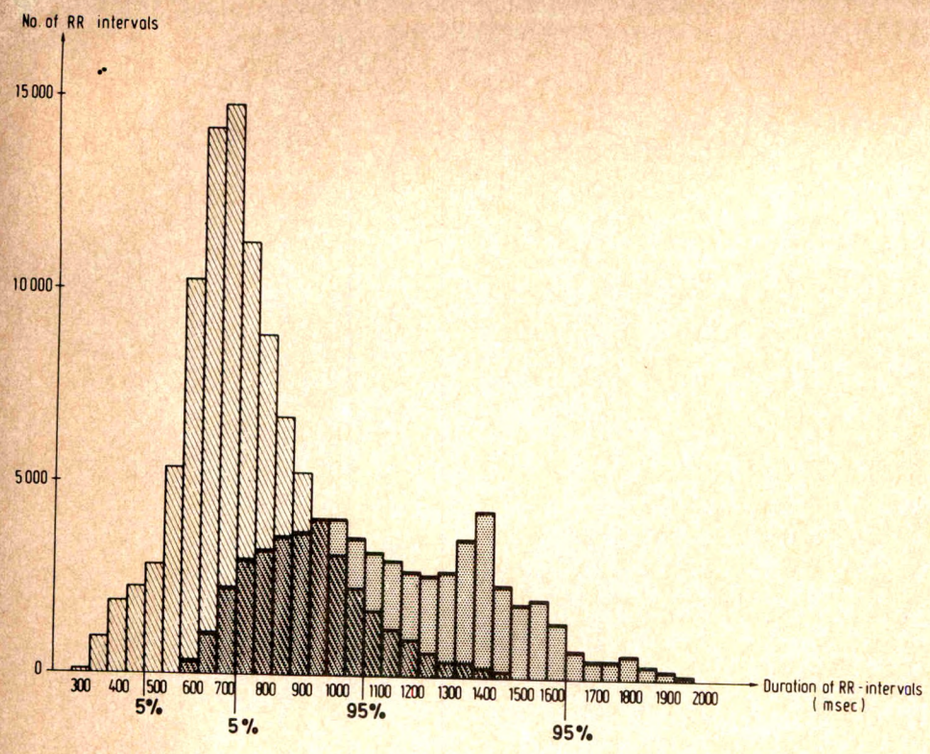

FIGURE 2. RR-interval histograms of patient 6. The recording time is 21 hours, 15 minutes. The **thin border** represents the control phase before medication and the **heavy line** represents the maintenance phase after 3 days of treatment with 90 mg 3 times daily. Fifth percentile values are taken as shortest and ninety-fifth percentile values as longest RR intervals.

RR intervals also decreased after maintenance therapy (Fig. 4, Table IV).

Effect on the fastest and on the slowest atrioventricular conduction times: The shortest (fifth percentile) and longest (ninety-fifth percentile) RR intervals increased proportionately in 5 patients; however, in 5 patients the long RR intervals increased more than the shortest ones (Fig. 3, Table II).

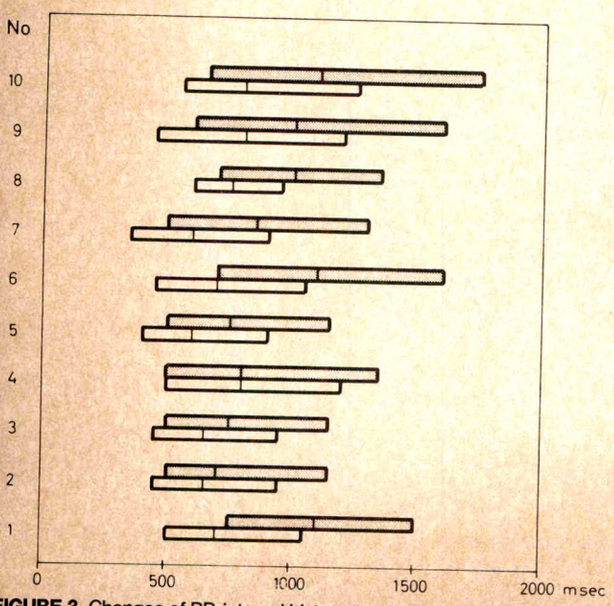

FIGURE 3. Changes of RR-interval histograms in the 10 patients studied. **Clear** and **shaded bars** represent control and maintenance phase histograms, respectively. The **horizontal columns** show only the characteristic parameters of the histograms: **left,** fifth percentile; **middle,** median value; **right,** ninety-fifth percentile.

Adverse effects: Patients 1 and 3 had a slight decrease in blood pressure during the acute test, but discontinuation of the therapy was not necessary. Pronounced cases of bradycardia were not observed. One of the 10 patients initially complained of fatigue. No further adverse effects were detected in the laboratory tests.

Discussion

In AF, the mean ventricular rate is determined by the extent of concealed conduction.[10–13] Owing to diminishing conduction and the formation of blocks, some atrial impulses penetrate in the AV node to varying degrees, without being conducted to the ventricle. According to Moe and Abildskov,[11] 2 factors determine the extent of concealed conduction: the AF rate, as input to the upper AV node, and the duration of the zone of concealment (ZOC). ZOC is the period after an atrial excitation during which concealed conduction can take place. Concealed conduction results in reduced conduction of atrial stimuli. It is the result of the complex 3-dimensional structure and of the electrophysiologic properties of the AV node cells.[14] The ramifications of these cells render summation, functional longitudinal dissociation and inhomogeneous fractionation of the propagating waves possible when several wave fronts coincide in AF, resulting in slow conduction and block formation.[15–17] In addition, local reentry phenomena are stimulated by the "blind cells."[18] The ZOC is not constant during AF. Although it depends on the refractory period of the AV node, the 2 variables are more or less equivalent only in very short RR intervals, when minimal or no concealed conduction takes place.[11,12] His bundle electrocardiographic studies of patients with AF indicate that the ZOC is essentially localized proximally to the His bundle.[19] Decreased conductivity would [illegible]

TABLE III Results of the Acute Test After 120 mg of Diltiazem

Pt	Onset of Effect (hours)	Duration of Effect (hours)	Initial Mean Ventricular Rate (beats/min)	Lowest Ventricular Rate (beats/min)	Reduction (%)	Plasma Concentration After 90 min (ng/ml)
1	1.00	8.66	90	56	38	30
2	3.00	3.66	92	66	28	37
3	2.83	5.66	90	62	31	17
4	2.33	5.66	88	60	32	34
5	1.50	7.33	96	74	23	75
6	2.00	5.66	80	60	25	...
7	1.66	...	100	68	32	44
8	1.83	5.33	84	64	24	59
9	2.66	5.33	80	52	35	2
10	1.12	5.00	86	54	37	...
Mean	2.00	5.33			30	
Range	1–3	3.66–8.5			23–38	

TABLE IV Reduction of RR Intervals After 3 Days of Maintenance Therapy with Diltiazem (90 mg 3 Times Daily)

Pt	Monitored Hours	No. of RR Intervals (mean ventricular rate, beats/min)		Reduction (%)
		Control	3 × 90 mg	
1	23.00	107,127 (78)	72,378 (52)	32
2	22.30	123,995 (92)	106,752 (79)	14
3	23.45	116,293 (83)	103,745 (74)	11
4	22.30	96,504 (71)	91,456 (68)	5
5	21.45	121,308 (95)	98,463 (75)	19
6	21.15	100,177 (76)	66,398 (50)	34
7	22.15	124,842 (95)	91,701 (69)	27
8	22.30	98,500 (78)	78,884 (61)	20
9	23.00	102,112 (74)	77,469 (56)	24
10	22.30	94,028 (71)	71,929 (53)	24

formation has been shown in the so-called AN and especially in the N regions of the AV node.[14,15] In the N region are calcium-influx-dependent, slow-response action potentials.[14,20] Calcium antagonists such as verapamil prolong AV conduction by acting on the slow-response action potentials of the AV node,[21–23] resulting in prolonged PR or AH intervals in sinus rhythm.[3,24] Verapamil therapy prolonged the functional refractory period of the AV node more than diltiazem.[25]

Intravenous diltiazem treatment causes a decrease in the mean ventricular rate in patients with AF.[9] In the 10 patients of this study, the mean ventricular rate was reduced significantly by a 120-mg single oral dose of diltiazem, as well as by maintenance treatment of 90 mg 3 times daily. It is concluded that reduction of the mean ventricular rate is possible by increasing concealed conduction in the AV node with oral administration of diltiazem, as with verapamil. The histogram of the RR intervals was analyzed to study the underlying mecha-

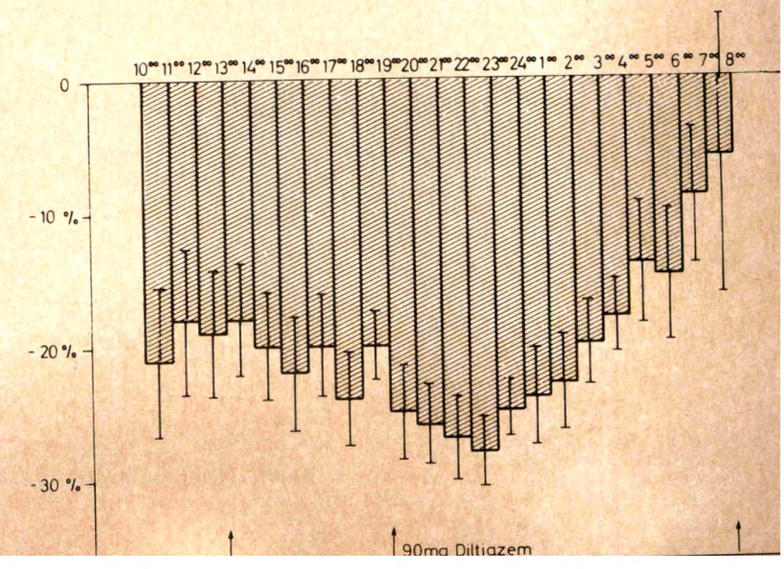

FIGURE 4. Changes of the RR intervals after diltiazem therapy for 3 days (90 mg 3 times daily). Average RR intervals have been calculated for each 1-hour interval for each patient. These are compared to the respective control values (before treatment). The depth of the columns represent the mean decrease of the heart rate in the 10 patients studied; bars show the standard deviation. Apparently the effect of the evening dose given at 7 PM does not last until next morning.

nism of the reduction of the mean ventricular rate. According to Moe and Abildskov,[11] the extent of concealed conduction is proportional to the duration of the ZOC and to the AF rate. Therefore, an increase in concealed conduction is furthered by an increase in AF rate and by the prolongation of the ZOC. An increase in concealed conduction in the AV node results in more excitations blocked and in longer and less regular RR intervals. Accordingly, the longest RR intervals contain a high proportion of concealed conduction, whereas the shortest RR intervals contain much less or no concealed conduction. The shortest RR intervals are largely determined by the functional AV refractory period, and coincide with it when there is no concealed conduction.[11] Consequently, the change of the RR-interval histogram after treatment may yield some information about the mechanisms involved.

In animals, influencing AV conduction by vagal stimulation results in enhancement of concealed conduction. AF rate, and consequently the number of impulses entering the AV node, increases as a result of the reduced atrial refractory period. The ZOC also increases; however, the functional refractory period of the AV node remains largely unchanged. This leads to a decrease in mean ventricular rate, while the RR intervals become longer and less regular. Yet the shortest RR intervals, which have little or no concealed conduction, do not disappear.[11] Digitalis exerts a similar influence on AV conduction in AF.[26] Adrenergic influence accelerates AV conduction and reduces the ZOC, and the ventricular rate becomes more rapid and regular.[11]

In this study, 50% of the patients responded to diltiazem maintenance therapy with proportional changes of the longest (ninety-fifth percentile) and shortest (fifth percentile) RR intervals, whereas the rest of the patients responded with a disproportionate increase of the longest RR intervals. After the administration of diltiazem, a shift of the shortest RR intervals to the right in the spectrum of an absolute arrhythmia suggests a change of the AV nodal refractory period, since the shortest RR intervals contain little or no concealed conduction. However, a proportional shift of the longest intervals suggests an increase in concealed conduction. The latter can be caused by accelerated AF rate or by an increase of the ZOC. A disproportionate increase of the longest RR intervals could be then attributed to increased concealed conduction. Since the shortest RR intervals reflecting the functional AV refractory period change less, the increase of concealed conduction is probably caused by accelerated atrial rate. This mechanism would resemble experimental vagal stimulation. However, proportionate change of the shortest and longest RR intervals suggest a similar increase of both AF rate and the AV nodal refractory period.

Influencing the AF rate in diseased atria by means of calcium antagonist drugs may be possible, since slow response action potentials have also been demonstrated there.[27] AF is generally caused by reentrant activity in the atrial region.[28] The extent to which calcium antagonists cause accelerated circulatory excitation and increased atrial rate is not well known. In the ischemic, damaged ventricular myocardium, verapamil has been shown to improve conduction, probably influencing depressed fast-response action potentials.[29] With diltiazem treatment, a decreased functional refractory period has been shown in the human atrium, which may result in accelerated conduction.[25] After administration of diltiazem we noted no pseudoregularization of the RR intervals in AF, as observed after administration of large doses of verapamil, and attributed to a possible total AV block and activity in an ectopic ventricular center.[5]

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Electrocardiographic Diagnosis of Left Ventricular Hypertrophy in the Presence of Left Bundle Branch Block: An Echocardiographic Study

HENRYK KAFKA, MD, GARY W. BURGGRAF, MD, and JOHN A. MILLIKEN, MD

This study tests the electrocardiographic diagnosis of left ventricular (LV) hypertrophy in the presence of left bundle branch block (BBB). The LV mass of 125 patients with left BBB was estimated by echocardiography. M-mode echocardiography was technically adequate in 80% of patients. LV mass was calculated using previously validated M-mode formulas and then indexed to body surface area. The known shifts in the QRS voltage and axis with the onset of left BBB led to the selection of 4 electrocardiographic parameters for the diagnosis of LV hypertrophy: R in aVL 11 or more; QRS axis −40° or less (or SII >RII); $SV_1 + RV_5$ to RV_6 40 or more; SV_2 30 or more and SV_3 25 or more; these parameters were used in cumulative fashion. This cumulative approach was superior to using single conventional criterion such as the $SV_1 + RV_5$ or RV_6. When LV hypertrophy was defined as an M-mode index of at least 115 g/m², the sensitivity was 75% and specificity 90%. Using an M-mode mass of at least 215 g as the standard, the sensitivity was 73% and the specificity 66%. LV hypertrophy can be diagnosed by electrocardiographic criteria in the presence of left BBB at least as reliably as in normal conduction.

(Am J Cardiol 1985;55:103–106)

The presence of left bundle branch block (BBB) is believed, by most electrocardiographers, to invalidate the usual criteria for left ventricular (LV) hypertrophy. However, several autopsy studies indicate that the commonly used criteria, as in normal conduction, remain specific but insensitive.[1–4] Since necropsy studies usually have few hearts of normal size, this tends to limit the usefulness of their conclusions. Both M-mode and 2-dimensional (2-D) echocardiography have been demonstrated to be valid methods for estimating LV mass.[5,6] Their use in patients with normal conduction suggests that the Romhilt-Estes point score[7] and the Sokolow-Lyon voltage criteria for the electrocardiographic diagnosis of LV hypertrophy are insensitive, although highly specific.[8,9] In most studies that evaluate electrocardiographic criteria for LV hypertrophy, those with prior myocardial infarction or left BBB are excluded because such disorders are believed to impair the electrocardiographic recognition of LV hypertrophy.[8,9] This study assesses the validity of electrocardiographic criteria in the diagnosis of LV hypertrophy in the presence of left BBB using echocardiographically determined LV mass as the standard.

From the Department of Medicine, Queen's University, Kingston, Ontario, Canada. Manuscript received July 9, 1984; revised manuscript received September 10, 1984, accepted September 11, 1984.

Address for reprints: John A. Milliken, MD, Department of Cardiology, Hotel Dieu Hospital, Kingston, Ontario, Canada K7L 3H6.

Methods

Study patients: The study group consisted of 125 patients (51 women, 74 men) with left BBB, aged 34 to 98 years (mean 66). The patients were selected from the electrocardiographic files of Hotel Dieu Hospital in 1982. Two hundred seventy-six patients were identified in this fashion, but only 125 could be recalled for echocardiography and a repeat electrocardiogram. Twenty-two of the 125 patients were clinically normal, 56 had suspected coronary artery disease, 16 had idiopathic cardiomyopathy, 10 had valvular heart disease, 16 had hypertension and 5 had other cardiac problems.

Another group of 41 clinically normal subjects with normal electrocardiograms were examined to establish a normal value for LV mass.

Electrocardiographic analysis: All electrocardiograms were recorded with either a Marquette Mac I or Mac II cart using multichannel simultaneous leads. The criteria used for selection of left bundle branch block were: QRS duration 120 ms or longer; broad, slurred R waves in leads I, aVL and V_6; and broad, slurred S waves in V_1 and V_2 (QS or rS). All electrocardiographic measurements were made manually and entered into the computer for subsequent analyses. The R and S waves of all 12 leads were carefully measured and recorded, averaging, where necessary, to the nearest 0.1 mV or mm. Axis

TABLE I Mean Left Ventricular Mass in 41 Normal Subjects and 100 Subjects with Left Bundle Branch Block

	Normal Subjects		Left BBB Subjects	
	M-Mode Mass (g)	M-Mode Mass Index* (g/m^2)	M-Mode Mass (g)	M-mode Mass Index (g/m^2)
Women	133 ± 26	81 ± 14	201 ± 74	125 ± 48
Men	169 ± 36†	86 ± 19	315 ± 54	168 ± 54
Whole group	150 ± 35	83 ± 16	259 ± 107	156 ± 101

Values are mean ± standard deviation.
* M-mode index was derived by dividing M-mode mass by body surface area.
† Significant difference ($p < 0.001$) between men and women.
BBB = bundle branch block.

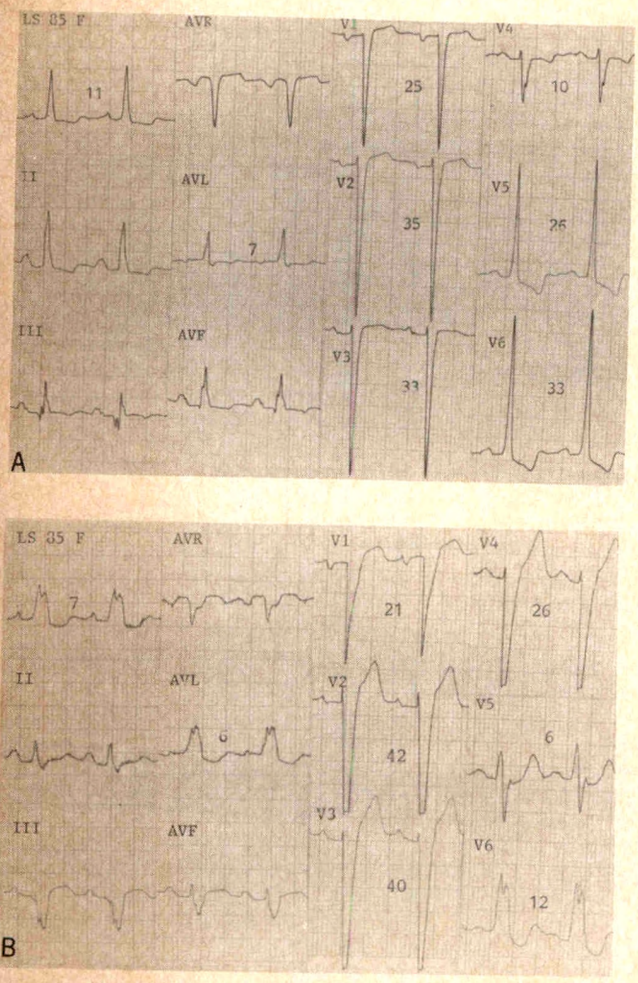

FIGURE 1. Transient left bundle branch block (BBB) reducing the voltage of the R wave in leads I, V_5 and V_6 and shifting the axis to the left. **A,** the high voltage of left ventricular hypertrophy in the chest leads shifts ($SV_1 + RV_6 = 58$). **B,** 2 days later left BBB is present ($SV_1 + RV_6 = 33$). The amplitude of the appropriate R and S waves are included on each graph. A repeat record at half normal standardization was needed where clipping is seen in leads V_1 to V_3 in panel **B.** Note the shift of the axis to the left and the deeper SV_2 (35 to 42), SV_3 (33 to 40) and SV_4 (10 to 26) with the onset of left BBB.

TABLE II The Percentage Sensitivity and Specificity of Various Electrocardiographic Measurements* of Left Ventricular Hypertrophy in Left Bundle Branch Block

	100 Subjects	
Left Ventricular Hypertrophy	M-Mode Mass ≥ 215g 56% Sens/Spec	M-Mode Index ≥115g/m^2 71% Sens/Spec
RI ≥13	9/95	8/97
RI + SIII ≥25	13/98	13/100
R aVL ≥11†	21/89	24/100
Lewis index ≥17	38/75	35/79
Axis ≤−30°	30/75	34/83
Axis ≤−40°†	23/85	28/100
SV_1 ≥30	29/89	28/97
SV_1 ≥24	46/55	48/62
SV_2 ≥30 and SV_3 ≥25†	46/80	48/93
SV_3 ≥25	57/77	56/90
RV_5 or RV_6 ≥25	4/100	3/100
$SV_1 + RV_5$ or RV_6 ≥35	55/73	51/76
$SV_1 + RV_5$ or RV_6 ≥40†	32/91	30/97
$SV_2 + RV_5$ or RV_6 ≥45	46/82	45/90
R + S ≥45‡	59/77	55/86
R + S ≥40‡	66/59	63/66
$RV_6 > RV_5$	68/7	75/10
Selvester score ≥15	35/80	35/86
Left atrial enlargement	41/98	41/93
QRS duration ≥0.16 second	68/25	75/34

* Reported in mm unless otherwise stated.
† Used subsequently in a cumulative fashion in Table III.
‡ Any precordial R and S.

direction was calculated from the limb lead measurements and recorded to the nearest 5° interval. The presence of left atrial enlargement[7] was independently diagnosed by 2 readers. The Lewis index [(RI − SI) + (SIII − RIII)], Sokolow-Lyon score ($SV_1 + RV_5$ or RV_6) and the Selvester score[10] were all calculated.

Echocardiographic technique: Echocardiograms were obtained with a Hewlett-Packard phased-array instrument (model 77020A) using a 2.5-MHz transducer. The LV mass was then calculated by the method of Reichek and Devereux,[8] and we defined LV hypertrophy as they did: LV mass of at least 215 g.[8] Rather than using only 1 value for LV mass, for both sexes and all ages, we also corrected for body size by dividing the calculated M-mode mass by the body surface area. LV hypertrophy was then defined as an M-mode mass index of at least 2 standard deviations of the mean mass index of our 41 normal subjects (Table I)—≥ 115 g/m^2.

Statistical methods: The sensitivity and specificity of various electrocardiographic criteria for LV hypertrophy were calculated using standard formulas: sensitivity (%) = (true-positives correctly diagnosed/total true positives) × 100; specificity (%) = (true-negatives correctly diagnosed/total true negatives) × 100.

Results

Satisfactory M-mode echocardiograms were obtained in all 41 normal subjects. The LV mass values for the normal subjects ranged from 75 to 215 g (mean ± 1 standard deviation 150 ± 35). The mean LV mass was lower for women than for men, but the use of the LV mass index eliminated this difference. Among those with left BBB, men had a much higher mean LV mass (315 g) than women (201 g). This difference was also reduced when the mass index figure was used: men, 168

g/m^2; women, 125 g/m^2. The mean figures for the left BBB group exceed the upper normal range by a considerable margin, resulting in 56% with an LV mass of 215 g or more and 71% with a mass index 115 g/m^2 or more.

Electrocardiographic criteria: The sensitivity and specificity of the various electrocardiographic parameters in the detection of LV hypertrophy is contained in Table II. Good overall single parameters were $SV_3 \geq 25$ (sensitivity 56% and specificity 90%) and $R + S \geq 40$ (sensitivity 63% and specificity 66%). A QRS duration of 0.16 or higher was very sensitive (75%), but specificity was low, 34%. Using the M-mode mass index of at least 115 g/m^2 as the standard for increased LV mass, various combinations of criteria were selected from Table II and used in cumulative fashion. Intermittent left BBB is known to alter voltage and shift electrical axis to the left, which led to the selection of 4 electrocardiographic parameters (Fig. 1).

Table III shows the effects of combining 4 criteria in cumulative fashion. Two criteria from the limb leads (R in aVL 11 or more and QRS axis −40 or less or SII > RII) correctly diagnosed 39% of those with LV hypertrophy with 100% specificity; and 17% were not detected by the subsequent use of chest lead measurements. Two chest lead measurements, Sokolow-Lyon index 40 or more and $SV_2 \geq 30$ and SV_3 25 or more, correctly labeled 56%, with a specificity of 93%. When any of these 4 parameters was accepted as a diagnosis of LV hypertrophy, the sensitivity was 75% and specificity 90%. If an LV mass 215 g or more was required as a standard, then the sensitivity remained at 73% but the specificity fell to 66%. The use of criteria for left atrial abnormality added only 3% to the sensitivity values with no loss of specificity.

TABLE III The Cumulative Percentage Sensitivity and Specificity for Left Ventricular Hypertrophy in Left Bundle Branch Block Using 4 Electrocardiographic Variables (n = 100)

Left Ventricular Hypertrophy	M-Mode Mass ≥215 g 56% Sens/Spec	M-Mode Index ≥115 g/m^2 71% Sens/Spec
RaVl ≥11 mm	21/89	24/100
Axis ≤−40° (or SII > RII)	34/80	39/100
$SV_1 + RV_5$ or $RV_6 \geq 40$ mm	55/75	58/97
$SV_2 \geq 30$ and $SV_3 \geq 25$ mm	73/66	75/90

Discussion

In 1951, Pantridge[11] used clinical assessment for proof of LV hypertrophy and concluded that the electrocardiographic criteria for left BBB with LV hypertrophy were not altered from those used in normal conduction. Most of the later studies have been limited to autopsied cases and contain few patients with a normal LV mass.[1–4,11,12] They are unlikely to be representative of the live population with left BBB. By using an echocardiographic standard, we could include patients with a wide range of LV weights. Many were normal; 44% had an LV mass of less than 215 g and 29% had a normal M-mode mass index of less than 115 g/m^2. This is in keeping with previously reported studies of ambulatory military patients with left BBB.[13,14]

In 1978, Lopes et al[15] studied 30 patients with left BBB by means of M-mode echocardiography and calculated the LV mass. In 23 patients with an abnormal left ventricle, the LV mass averaged 241 ± 12 g. The 7 patients with a normal left ventricle had an LV mass of 138 ± 6 g. The Sokolow-Lyon score diagnosed 19 of 23 (82%) with 2 false-positive results. Five patients had intermittent left BBB and all had an increase in SV_1 and a decrease in RV_5 and RV_6 when left BBB was present. The Sokolow-Lyon score, however, was unaltered.

Recently, Noble et al[16] used M-mode echocardiography to determine the prevalence of anatomic LV hypertrophy in 28 patients with left BBB. They found anatomic LV hypertrophy (defined as LV mass of 215 g or more) in 89% of their patients and left atrial abnormality detected 58%, with 100% specificity.

When left BBB occurs, both the QRS voltage and the QRS axis change from that seen during normal conduction. By reviewing 79 cases of intermittent left BBB, Cokkinos et al[17] found a statistically significant reduction in R-wave voltage in leads I, V_5 and V_6 and an increase in the S-wave voltage in V_1 and V_2 plus a leftward shift in the QRS axis. These changes apparently did not affect the Sokolow-Lyon score, so they concluded that this score was just as useful as in normal conduction. However, a Sokolow-Lyon value of more than 35 developed in 25%, thus reducing the specificity. The change in QRS axis was reported to be of little help.

Since LV mass may depend on body size,[18,19] it was indexed to body surface area. Our upper limit for a normal mass index by M-mode echocardiography, 115 g/m^2, compares with the value of 119 g/m^2 reported by others.[20] Despite the concern about the effect of body size on heart weight, Reichek and Devereux[8] used a value of 215 g for defining LV hypertrophy in their echocardiographic study of patients with normal conduction. We therefore used this criterion in our study.

Our sensitivities and specificities of individual variables in the detection of LV hypertrophy are similar to those reported by others[4,8,21] (Table IV). This confirms that electrocardiographic criteria are as valid in the presence of left BBB as they are in normal conduction. Most previous studies have used only individual electrocardiographic variables and never combined them cumulatively like the usual reader. Our 4 criteria all exceed the 98th percentile normal ranges studied and reviewed recently by Murphy et al.[22] The voltage shifts known to occur in left BBB undoubtedly enhance the validity of these measurements. This and the marked increase in LV mass in many of our BBB patients may account for our higher sensitivity.

Recently Teichholz et al[23] used stepwise discriminant analysis to improve the electrocardiographic criteria for the diagnosis of LV hypertrophy in normal conduction.

TABLE IV Comparison of Selected Electrocardiographic Criteria for Left Ventricular Hypertrophy in Left Bundle Branch Block and in Normal Conduction

	Echo Studies		Autopsy Studies	
	Present Study—Left BBB, LV Mass ≥215 g Sens/Spec	Reichek[8]—Normal Conduction, LV Mass ≥215 g Sens/Spec	Havelda[4]—Left BBB, LV Weight >250 g Sens/Spec	Romhilt[21]—Normal Conduction, LV Weight >175 g Sens/Spec
R aVL ≥11	21/89	47/99	36/83	13/99
Lewis index ≥17	38/75		34/100	18/98
$SV_1 + RV_5$ or RV_6 ≥35	55/73	53/86	37/89	56/88
Left atrial enlargement	41/98	47/91		48/95*
Left axis ≤−30	30/75	33/97	39/91	24/87

* From Romhilt and Estes.[7]

Their sensitivity increased from 42% to 78%, while specificity decreased from 86% to 76%. They had comparable results when their program was retested in a new group of patients. Multivariate discriminant analysis may also help in left BBB.

By using 4 relatively simple electrocardiographic measurements, one should be able to diagnose LV hypertrophy in the presence of left BBB with a sensitivity of 75% and specificity of 90%. These criteria must be tested in a new group of cases with left BBB.

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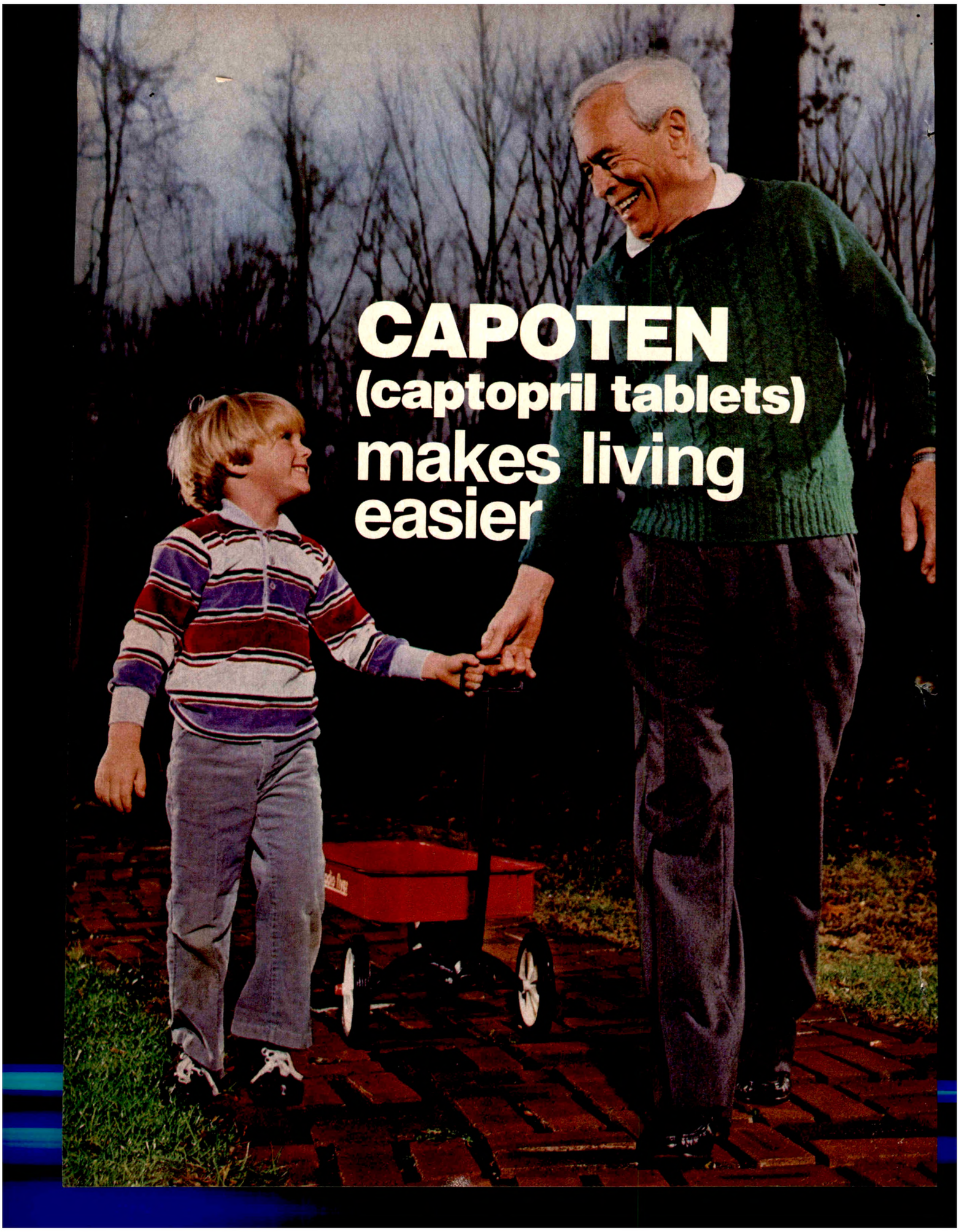
Heart failure makes
life more difficult


CAPOTEN
(captopril tablets)
makes living
easier

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ACE* INHIBITOR

CAPOTEN®
(captopril tablets)

Can make the difference between merely existing and actively living

With the availability of CAPOTEN, heart failure† patients can enjoy an enhanced quality of life. Because, in patients who require more than digitalis and diuretics, CAPOTEN can improve their hemodynamic profile[1] and provide an opportunity to feel better.

- Eases principal heart failure symptoms[1]
- Restores patients' sense of well-being[1]
- Increases patients' capacity for exercise[1], allowing them to participate more fully in the physical activities of everyday life

†CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

*Angiotensin Converting Enzyme

Please see brief summary of prescribing information on last pages of this advertisement.

CAPOTEN
Your First Choice After Digitalis and Diuretics

ACE*INHIBITOR

CAPOTEN®
(captopril tablets)

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

- **Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.**
- **Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.**
- **Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.**
- **The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.**

*Angiotensin Converting Enzyme

†Please see brief summary of prescribing information on last pages of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Data on file, Squibb Institute for Medical Research.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.
Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.
WARNINGS: Proteinuria — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.
Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.
PRECAUTION: General: *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.
Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.
Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.
Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.
Agents Causing Renin Release — Captopril's effect will be augmented by

 (Continued on next page.)

(continued from preceding page)

antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal — One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic — Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients — reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia — About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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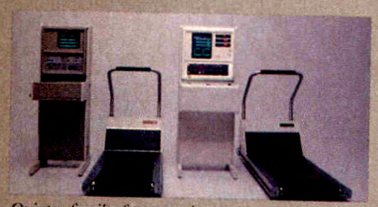

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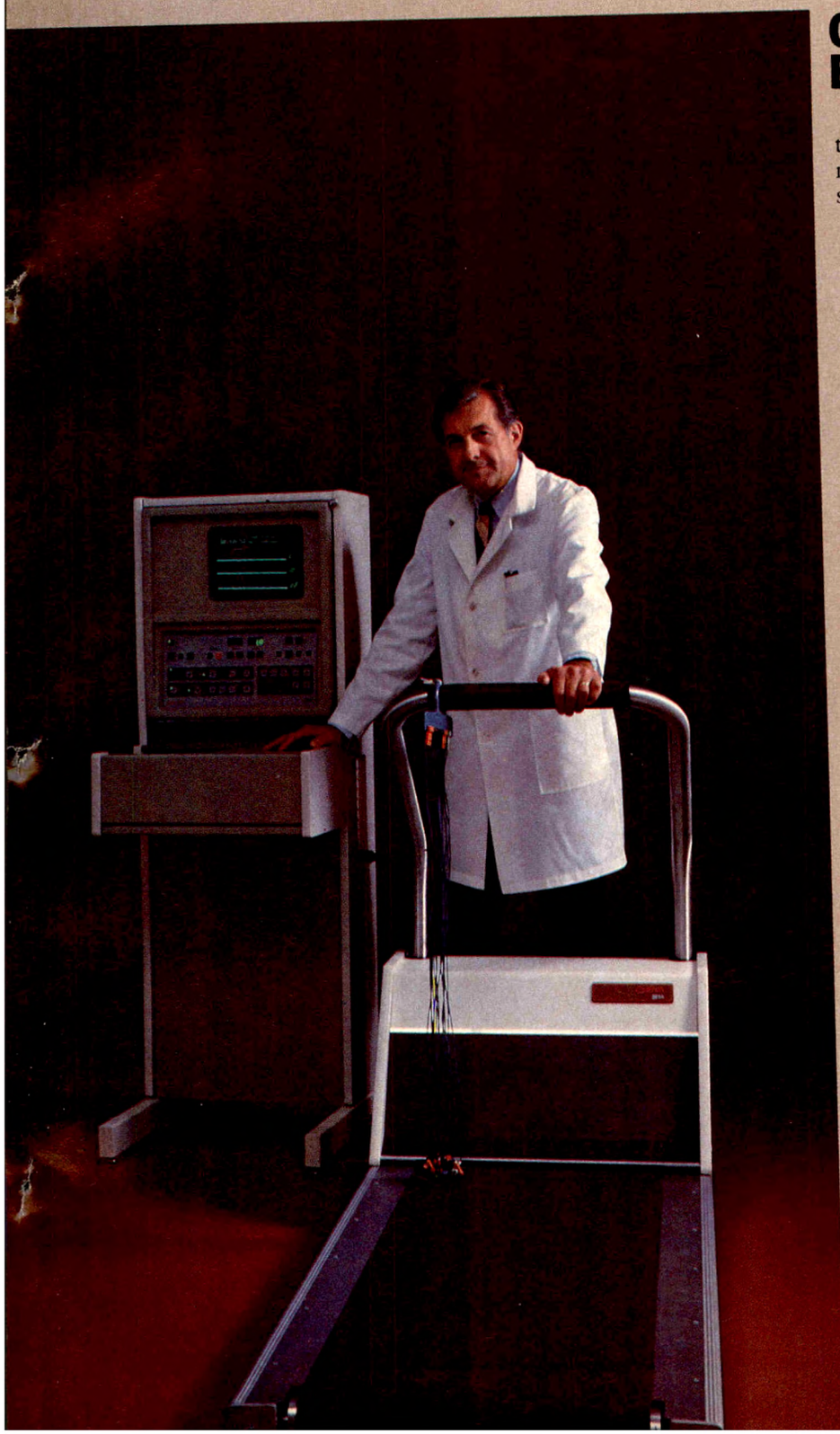

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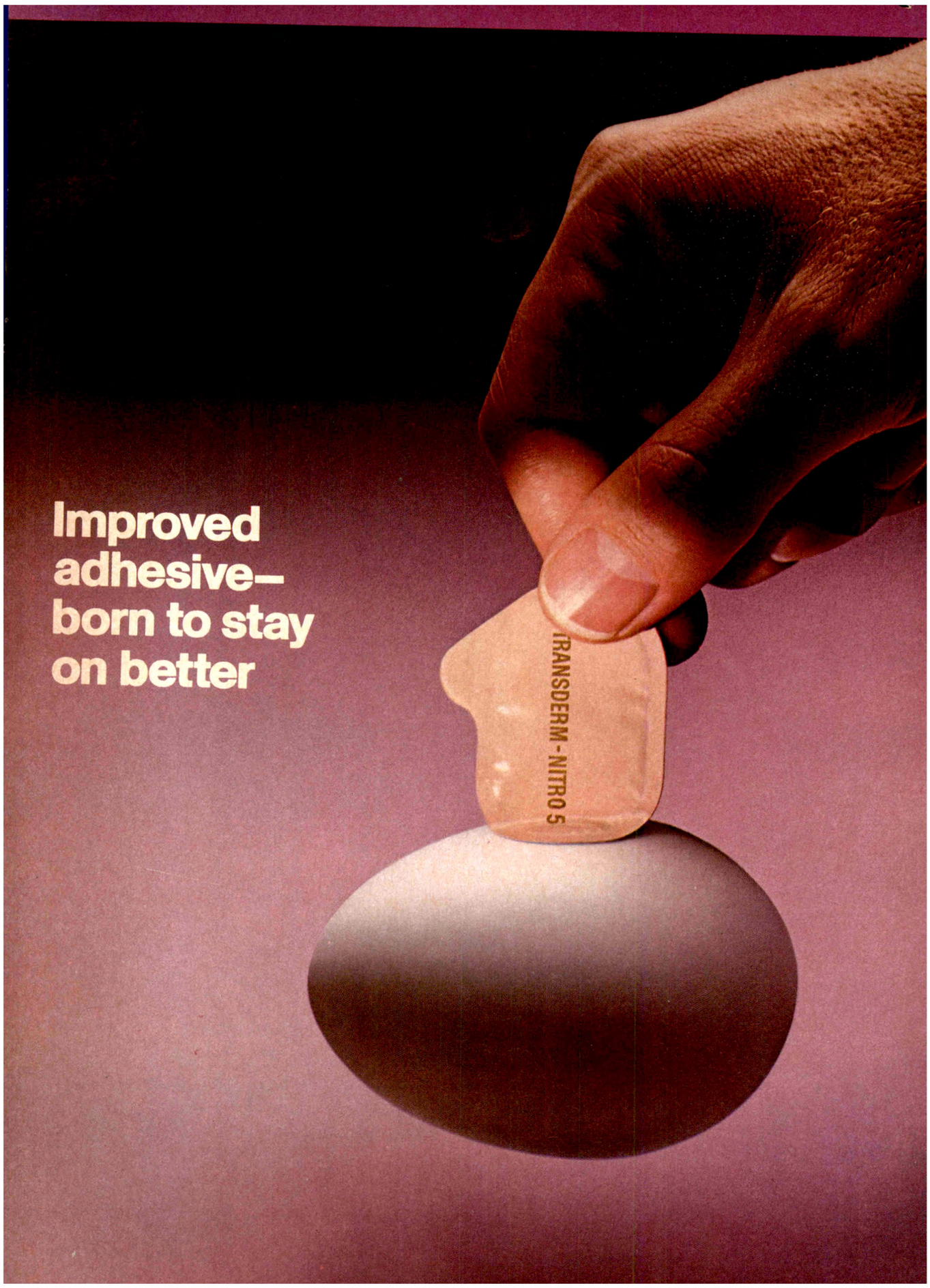
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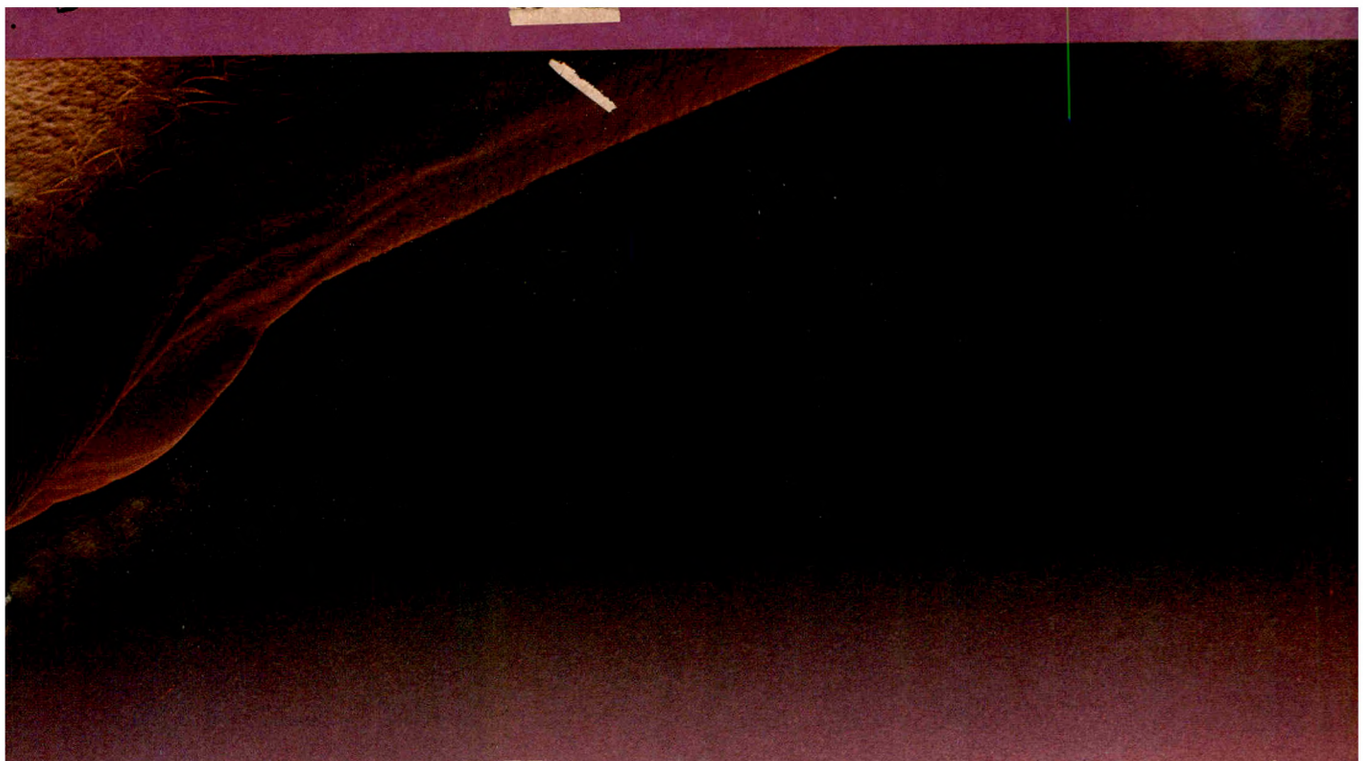

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nitroglycerin 24-hr systems: 2.5 mg, 5 mg, 10 mg, 15 mg

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Stays on better

Reformulated adhesive delivers optimum staying power. Results of two studies* with both placebo and active systems on normal subjects proved that Transderm-Nitro has an almost 100% adhesion rate, even under the most adverse conditions, including hot, humid summer weather.

Handles better

Clear plastic 3M backing is easy to remove—practically slides right off. There's no risk of your patient damaging the system. Especially easy to handle for elderly patients.

Comes off without significant irritation

The reformulated adhesive is strong, yet gentle on the skin. The studies* also showed no significant irritation after removal.

Contraindicated in patients with intolerance to organic nitrate drugs.

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA. (See Brief Summary of Prescribing Information on the next page.)

*Data on file, CIBA Pharmaceutical Co.

Transderm®-Nitro

(nitroglycerin)
Transdermal Therapeutic System

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)*

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
2.5 mg/24 hr	12.5 mg	5 cm^2	30 Systems (NDC 0083-2025-26)
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)
15 mg/24 hr	75 mg	30 cm^2	30 Systems (NDC 0083-2115-26)

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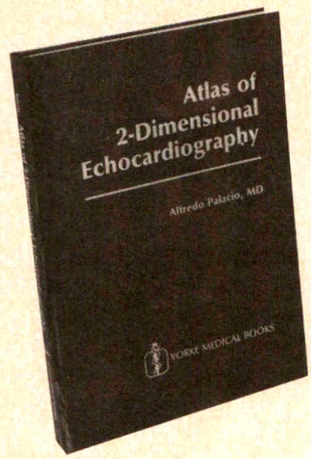

Atlas of 2-Dimensional Echocardiography

by Alfredo Palacio, MD
Director of National Institute of Cardiology, Guayaquil, Ecuador

Foreword by David H. Spodick, MD, DSc
Professor of Medicine, University of Massachusetts Medical School; Director, Division of Cardiology, St. Vincent Hospital, Worcester, Massachusetts

ISBN 0-914316-35,4, 198pp., illus., large format
8¼ x 12, March '83, $69.00

2-dimensional echocardiography complemented by M-mode echocardiography has become one of the most common noninvasive diagnostic tools used by the cardiologist. With publication of the ATLAS of 2-DIMENSIONAL ECHOCARDIOGRAPHY, neophyte and expert alike now have available to them the most truly usable didactic presentation of the subject ever published.

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Serial Measurements of Systolic Time Intervals During Treatment with Hydrochlorothiazide Alone and Combined with Other Antihypertensive Agents

MARY C. KYLE, MS, and EDWARD D. FREIS, MD

As part of the Veterans Administration cooperative studies on antihypertensive agents, systolic time intervals (STIs) were recorded before and after 2 or 4 weeks of treatment with hydrochlorothiazide (HCTZ) alone in 320 asymptomatic patients with mild to moderate hypertension. After treatment with HCTZ, left ventricular ejection time corrected for heart rate (ΔLVET) was significantly reduced. This decrease is consistent with other hemodynamic observations indicating a reduced preload and stroke volume after administration of thiazides. Electromechanical systole corrected for heart rate (ΔQS_2) decreased, while the ratio of preejection period to LVET (PEP/LVET) increased, reflecting reduced left ventricular function. PEP did not change. Four step 2 drugs—hydralazine, prazosin, oxprenolol and propranolol—were then added randomly to HCTZ and further recordings of STIs were taken at 1 and 6 months after administration of these drugs. The ΔLVET and ΔQS_2 increased and PEP/LVET decreased, suggesting improved left ventricular function after administration of all 4 agents. These changes may have been due to the added agents or to the recovery of cardiac output that occurs independently during long-term treatment with thiazide diuretic drugs alone. PEP decreased slightly after hydralazine and prazosin and increased slightly after treatment with the β-blocking drugs, although none of these changes were significant except those during hydralazine treatment. Processing of the STIs was greatly facilitated by the automated system for recording and analyzing the measurements.

(Am J Cardiol 1985;55:107–111)

Changes in systolic time intervals (STI) have been reported with a variety of cardiovascular agents.[1] Most of these studies have explored the effects of single doses and few have been concerned with the effects of long-term administration of cardiovascular agents on STI. Some drugs with important effects on the cardiovascular system, such as the thiazide diuretic drugs, have been little studied with STI. The present study presents the effects of hydrochlorothiazide (HCTZ) on left ventricular performance in hypertensive patients as determined by STI.

Methods

The subjects were male hypertensive patients enrolled in 2 Veterans Administration Cooperative Studies.[2,3] Both studies evaluated various step 2 antihypertensive agents in patients whose diastolic blood pressures (BP) were not reduced to below 90 mm Hg with HCTZ alone. In the study in which hydralazine (30 to 150 mg/day) or prazosin (3 to 15 mg/day) were added, the period of treatment with HCTZ alone (75 mg/day) was 2 weeks.[2] In the study with oxprenolol or propranolol (120 to 360 mg/day), it was 4 weeks.[3] HCTZ and the step 2 agents were administered in divided doses 3 times daily.

The range of sitting diastolic BP required for admission to both studies was 95 to 114 mm Hg as the average of the last 2 biweekly visits during a 4- to 8-week pretreatment placebo period.[2,3] Patients with severe complications of hypertension and noncompliant patients (determined by placebo pill counts) were excluded.

There were no significant differences in the characteristics of the 2 groups of patients. The average age was 51 years and exclusion criteria were essentially the same in both studies. The racial distribution, blood chemistry levels and heart rate also were comparable in the 2 groups. Because of the similar characteristics, it was considered valid to compare the results of the 2 studies with respect to the effects of HCTZ per se.

In the hydralazine-prazosin study, 163 patients had satisfactory recordings of STIs before and after 2 weeks of treat-

From the Veterans Administration Cooperative Study Group on Antihypertensive Agents, Veterans Administration and Georgetown University Medical Centers, Washington, D.C. Manuscript received June 27, 1984; revised manuscript received August 31, 1984, accepted September 4, 1984.

Address for reprints: Edward D. Freis, MD, Veterans Administration Medical Center, 50 Irving Street, NW, Washington, D.C. 20422

TABLE I Mean Changes in Systolic Time Intervals 2 Weeks and 4 Weeks After Hydrochlorothiazide*

Measurement	HCTZ 2 Weeks (n = 163) Placebo	HCTZ 2 Weeks (n = 163) After HCTZ	HCTZ 4 Weeks (n = 157) Placebo	HCTZ 4 Weeks (n = 157) After HCTZ
Diastolic BP (mm Hg)	105 ± 0	−5 ± 0†	104 ± 0	−4 ± 1†
Heart rate (beats/min)	69 ± 1	+3 ± 1†	69 ± 1	+2 ± 1‡
ΔQS_2 (ms)	21 ± 1	−15 ± 1†	19 ± 1	−12 ± 1†
ΔLVET (ms)	3 ± 1	−16 ± 1†	3 ± 1	−14 ± 1†
PEP (ms)	115 ± 1	0 ± 1	113 ± 1	+2 ± 1
PEP/LVET	0.40 ± 0	+0.03 ± 0†	0.39 ± 0	+0.03 ± 0†

* Values are mean ± standard error of the mean.
† $p \leq 0.001$; ‡ $p \leq 0.01$.
BP = blood pressure; HCTZ = hydrochlorothiazide; ΔLVET = left ventricular ejection time corrected for heart rate; PEP = preejection period; ΔQS_2 = electromechanical systole corrected for heart rate.

ment with HCTZ alone and in the oxprenolol-propranolol study, 157 patients had satisfactory recordings after 4 weeks of treatment with HCTZ alone. After the recordings were obtained, patients were then randomly assigned double-blind to 1 of the step 2 drugs and further recordings of STI were taken 1 and 6 months after randomization.

The STI were determined from simultaneous tape recordings of the electrocardiogram, phonocardiogram and the external carotid pulse wave taken in the supine position.[4] The recordings were taken at approximately the same time of day to avoid diurnal variations.[1] Blood pressure readings were taken in the right arm by means of a standard sphygmomanometer 3 times in the sitting position and the average was recorded.

The computer program for measuring STI[5,6] uses digitized data and pattern recognition algorithms to identify the salient points in the electrocardiogram, phonocardiogram and carotid pulse wave. When tested in 142 subjects, it showed close agreement with visual measurements.[5] The program for measuring STI has been incorporated into a self-contained and mobile, microcomputer-based, portable system[6] that provides immediate readout not only of STI, but also an analysis of the electrocardiogram.[7] This system displays the STI waveforms with markers where the computer identified the important landmarks and then presents a complete report containing the various STI indexes and demographic information.

Values for left ventricular ejection time (LVET) and electromechanical systole (QS_2) were corrected for heart rate and were expressed as ΔQS_2 and ΔLVET, which represent the differences between the observed values and those predicted from the regression equation relating QS_2 or LVET and heart rate as derived from a previous series of 199 normal male subjects.[4] Preejection period (PEP) and PEP/LVET were not corrected because of the small correlation observed between PEP and heart rate and because of evidence from acute studies indicating that PEP should not be adjusted for heart rate.[4]

Results

Hydrochlorothiazide alone: The average decrease in diastolic BP with HCTZ alone was 5 mm Hg in the 2-week trial and 4 mm Hg in the 4-week trial. After 2 and 4 weeks of treatment with HCTZ, mean heart rate increased 3 and 2 beats/min, respectively. All of these changes were significant (Table I). There was also a significant decrease in ΔLVET averaging 16 and 14 ms, respectively, in the 2- and 4-week studies ($p < 0.001$). PEP remained essentially unchanged. ΔQS_2 also decreased while the ratio PEP/LVET increased significantly. The reductions in ΔLVET and ΔQS_2 were slightly greater at 2 weeks than at 4 weeks after beginning treatment, although the difference was significant only with respect to ΔQS_2 ($p < 0.05$).

Addition of hydralazine: Compared with the levels of diastolic BP attained with HCTZ alone, a further reduction, averaging 7 mm Hg at 1 month and 8 mm Hg at 6 months, was achieved after the addition of hydralazine (Table II). Average heart rate was essentially unchanged.

The decrease in ΔLVET that occurred after therapy with HCTZ alone was partially reversed after the addition of hydralazine. The increase from HCTZ alone was 11 ms at 6 months, which was greater than the 4-ms increase at 1 month. The change at 6 months was 5 ms short of complete return to pretreatment levels. PEP decreased 4 ms from the HCTZ level at both 1 and 6 months. Due to the compensating changes in ΔLVET and PEP, ΔQS_2 remained unchanged at 1 month but increased at 6 months, reflecting the greater increase in ΔLVET at that time. PEP/LVET decreased significantly, returning approximately to baseline values.

Addition of prazosin: The decrease in diastolic BP with the addition of prazosin was the same as that with hydralazine (Table II). Heart rate decreased slightly. The ΔLVET increased, paralleling the changes seen in the hydralazine group. The return toward pretreatment levels was significantly greater at 6 months than at 1 month after the addition of prazosin ($p < 0.01$). As a result, ΔQS_2 at the 6-month recording also increased significantly from the level with HCTZ alone. PEP decreased slightly, but the changes were not significant. PEP/LVET also decreased significantly.

Addition of propranolol: Compared with the effect of HCTZ alone, the reduction of diastolic BP after therapy with propranolol was slightly greater than that with the other drugs, averaging 9 mm Hg at 1 month and 11 mm Hg at 6 months (Table III). Heart rate decreased 11 beats/min. As with hydralazine and prazosin, ΔLVET increased significantly, the increase again being slightly greater at 6 months than at 1 month. As was also noted during therapy with the other agents, the recovery to pretreatment levels was not complete. The ΔQS_2 also increased significantly, reflecting the change in ΔLVET. PEP increased slightly but not significantly. A significant reduction in PEP/LVET occurred, similar to the change observed with hydralazine and prazosin.

Addition of oxprenolol: Reductions in diastolic BP and heart rate were slightly less with oxprenolol than with propranolol (Table III). The ΔLVET again increased significantly and PEP increased slightly but not significantly. The ΔQS_2 increased significantly and PEP/LVET decreased.

Discussion

After diuretic treatment the major changes in left ventricular performance as judged by STI were a decrease in ΔLVET and ΔQS_2 and a concurrent increase

TABLE II Mean Changes in Systolic Time Intervals After Addition of Hydralazine or Prazosin to Hydrochlorothiazide*

Measurement	HCTZ Plus Hydralazine (n = 80)			HCTZ Plus Prazosin (n = 70)		
	HCTZ Alone	Change from HCTZ Alone		HCTZ Alone	Change from HCTZ Alone	
		At 1 Month	At 6 Months		At 1 Month	At 6 Months
Diastolic BP (mm Hg)	99 ± 1	−7 ± 1†	−8 ± 1†	100 ± 1	−7 ± 1†	−8 ± 1†
Heart rate (beats/min)	72 ± 1	+1 ± 1	−1 ± 1	71 ± 1	−2 ± 1	−3 ± 1§
ΔQS_2 (ms)	7 ± 2	0 ± 1	+6 ± 2†	4 ± 2	+1 ± 2	+7 ± 2†
ΔLVET (ms)	−13 ± 2	+4 ± 1‡	+11 ± 2†	−12 ± 2	+4 ± 2§	+9 ± 2†
PEP (ms)	116 ± 2	−4 ± 1‡	−4 ± 2§	113 ± 2	−3 ± 1	−1 ± 1
PEP/LVET	0.43 ± 0.01	−0.02 ± 0.01‡	−0.03 ± 0.01†	0.42 ± 0.01	−0.02 ± 0.01§	−0.02 ± 0.01§

* Values are expressed as mean ± standard error of the mean.
† $p \leq 0.001$; ‡ $p \leq 0.01$; § $p \leq 0.05$.
Abbreviations as in Table I.

TABLE III Mean Changes in Systolic Time Intervals After Addition of Oxprenolol or Propranolol to Hydrochlorothiazide*

Measurement	HCTZ Plus Oxprenolol (n = 77)			HCTZ Plus Propranolol (n = 69)		
	HCTZ Alone	Change from HCTZ Alone		HCTZ Alone	Change from HCTZ Alone	
		At 1 Month	At 6 Months		At 1 Month	At 6 Months
Diastolic BP (mm Hg)	100 ± 1	−8 ± 1†	−8 ± 1†	101 ± 1	−9 ± 1†	−11 ± 1†
Heart rate (beats/min)	71 ± 1	−6 ± 1†	−6 ± 1†	71 ± 1	−11 ± 1†	−11 ± 1†
ΔQS_2 (ms)	6 ± 2	+8 ± 2†	+9 ± 2†	8 ± 2	+8 ± 2†	+7 ± 2‡
ΔLVET (ms)	−11 ± 2	+8 ± 2†	+8 ± 2†	−11 ± 2	+9 ± 2†	+11 ± 2†
PEP (ms)	113 ± 2	+2 ± 1	+3 ± 2	116 ± 2	+3 ± 2	+1 ± 2
PEP/LVET	0.42 ± 0.01	−0.02 ± 0.01§	−0.01 ± 0.01	0.42 ± 0.01	−0.02 ± 0.01‡	−0.03 ± 0.01†

* Values are mean ± standard error of the mean.
† $p \leq 0.001$; ‡ $p \leq 0.01$; § $p \leq 0.05$.
Abbreviations as in Table I.

in PEP/LVET, without a significant change in PEP. Gonzalez-Gomez et al[8] reported significant decreases in LVET and QS_2 corrected for heart rate, with no significant increase in corrected PEP. Ejection time may decrease because diuretic drugs reduce plasma and interstitial fluid volumes, resulting in a decrease in venous pressure, preload and cardiac output.[9,10] Other interventions that reduce preload, such as upright tilting and venous tourniquets, also decrease LVET.[11,12] According to Stafford et al,[12] the shortening of the ejection time during upright tilt is probably secondary to the decrease in preload and end-diastolic volume.

Despite similar changes in LVET, the effects of thiazide diuretic drugs differ from those produced by upright tilting or venous tourniquets in that PEP remained unchanged after the diuretic drug, but was prolonged during upright tilting.[12] This difference may be related to 2 factors: (1) The reduction in supine preload may not be as great after diuretic therapy as during orthostasis, and (2) diastolic BP increases with tilting, increasing PEP, and decreases with diuretic drugs, decreasing PEP. The combination of a shortened LVET without compensatory increase in PEP may occur during various drug interventions.[13]

Pretreatment levels of PEP/LVET for these hypertensive patients were significantly higher ($p < 0.001$) than our normal value of 0.345,[4] and increased further after HCTZ. Thus, these patients probably had decreased left ventricular global performance at baseline as reflected by PEP/LVET and it was further reduced after HCTZ. The ΔQS_2 decreased significantly after HCTZ, possibly reflecting increased adrenergic activity induced by the decrease in plasma volume.

The effects of adding hydralazine or prazosin on the STI were similar. Changes after oxprenolol also were similar to those after propranolol, except for a lesser decrease in heart rate after oxprenolol. To simplify the discussion, the results with hydralazine and prazosin are considered as a unit for comparison with the 2 β-blocking drugs.

Diastolic BP decreased similarly with both hydralazine-prazosin and oxprenolol. The decrease was somewhat greater with propranolol, particularly after 6 months. Heart rate decreased with the β-blocking drugs and remained unchanged with hydralazine-prazosin. An increase in ΔLVET from the depressed levels noted with HCTZ alone was noted with all 4 step 2 drugs. The effects of continuous treatment with hydralazine or prazosin alone on the STI is unknown. After propranolol was given to patients with coronary heart disease[14,15] or hypertension[8] and to normal subjects,[16] corrected LVET either did not change significantly or decreased. During long-term treatment with propranolol, ΔLVET remains unchanged from pretreatment levels.[4]

Left ventricular function improved over the long term with step 2 drugs. This was manifested principally by a decrease in PEP/LVET with all 4 of the step 2 regimens. However, the values did not go lower than those

observed during pretreatment. The ΔLVET increased from the moderately depressed levels during short-term treatment with HCTZ alone, probably reflecting a return in left ventricular stroke volume. The increase in ΔQS_2 is consistent with resetting of the adrenergic system during long-term treatment.

PEP decreased slightly after hydralazine-prazosin treatment and increased slightly after the β-adrenergic drug treatment. None of these changes were significant except those during hydralazine treatment. The changes, although minor, were in the expected direction. Hydralazine alone shortens PEP, reflecting its positive inotropic effect,[17] whereas propranolol alone prolongs PEP both acutely[1,16] and after long-term treatment[4] by inhibiting adrenergic stimulation. However, in the long-term study, propranolol plus HCTZ resulted in no change in PEP. This effect of added HCTZ may have been a result of the significantly lower diastolic BP with the combined drugs than with propranolol alone.[4] In the present study the addition of β-blocking drugs resulted in a slight, although insignificant increase in PEP as compared with thiazide alone, which may reflect the opposing influences of reduced adrenergic drive on the one hand and of additional reduction of diastolic BP on the other.

As previously indicated, thiazide diuretic drugs have widely different hemodynamic effects during short-term compared with long-term treatment. During short-term treatment reductions are found in plasma volume, total extracellular volume[9] and cardiac output while total peripheral resistance increases or remains unchanged.[10] These early changes appear to be the direct result of reduced preload. After long-term treatment, despite a continued reduction in volume,[9,18,19] cardiac output returns to normal and total peripheral resistance decreases.[20–22] The mechanism remains unclear for the time-dependent return to a more physiologic hemodynamic state despite continued volume reduction.[22]

In the present study, the changes in STI observed with thiazide alone probably reflect predominantly short-term responses, whereas the changes observed with combined therapy probably represent long-term effects of HCTZ. The improvement in left ventricular performance after the addition of all 4 step 2 drugs may have been caused by the effects of the added drugs, but it also may reflect the long-term response to diuretic drugs per se.

The present results indicate that measurements of STIs are a sensitive indicator of the cardiac effects of the thiazide diuretic drugs. The significant reductions in ΔLVET and ΔQS_2 and the increase in PEP/LVET are consistent with the known short-term hemodynamic effects of the thiazides. The long-term return of these indexes toward pretreatment levels, although possibly influenced by the addition of other drugs, also is consistent with the long-term hemodynamic effects of the diuretic agents.

STI measurements and analysis were greatly facilitated by the use of automated methods, which provided a rapid and accurate method for processing a large volume of records. The present study demonstrates that STIs provide a useful noninvasive method for identifying functional cardiac changes associated with antihypertensive drug treatment studies.

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Appendix

Hydrochlorothiazide-Prazosin-Hydralazine Study

Chairman: Eli A. Ramirez, MD

Participants, Stations, Participating Investigators, Nurses and STI Technician: Jackson, MS: Leo Elson, MD (deceased), Milos Ulrych, MD, Pauline Derrington, RN; Washington, DC: Edward D. Freis, MD, Barbara Gregory, RN, Madeline Metcalfe, RN, Merdia Barnes; Miami, FL: James Oster, MD, Chea Haran, RN, Mary Smith, RN; Memphis, TN: Thomas J. White, MD, Susan Reece, RN; Allen Park, MI: Frederick Talmers, MD, Julie Pawelak, RN; San Juan, Puerto Rico: Eli A. Ramirez, MD, Maria H. Natal, RN.

Executive Committee: Eli A. Ramirez, MD (Chairman), Frederick Talmers, MD, Milos Ulrych, MD, J. R. Thomas, MD, Thomas J. White, MD, James Oster, MD, Edward D. Freis, MD, Harold W. Schnaper, MD, Lawrence Shaw, H. Mitchell Perry, MD.

Operations Committee: Sibley W. Hoobler, MD (Chairman), W. McFate Smith, MD C. Morton Hawkins, ScD.

Hydrochlorothiazide-Oxprenolol-Propranolol Study

Chairman: J. R. Thomas, MD

Participants, Stations, Participating Investigators, Nurses and STI Technician: Jackson, MS: Leo Elson, MD (deceased), Milos Ulrych, MD, Carol Wigley, Pauline Derrington; Washington, DC: Edward D. Freis, MD, Sally Shaughnessy, Barbara Gregory, Madeline Mecalfe, Merdia Barnes; Miami, FL: James Oster, MD, Chea Haran, Mary Smith; San Juan, Puerto Rico: Eli A. Ramirez, MD, Maria Natal; Memphis, TN: Thomas White, MD, Susan Reece, Jane Bowen; Allen Park, MI: Frederick Talmers, MD, Julie Pawelak.

Executive Committee: J. R. Thomas, MD, (Chairman), Eli A. Ramirez, MD, Edward D. Freis, MD, Leo Elson, MD (deceased), James Oster, MD, Frederick Talmers, MD, Thomas J. White, MD.

Operations Committee: Sibley Hoobler, MD (Chairman), William Smith, MD, Morton Hawkins, MD.

Both Studies

Biostatistics and Research Data Processing: Hines Cooperative Studies Program Coordinating Center, Hines, IL. Chiefs: Kenneth E. James, PhD, William G. Henderson, PhD; Study Biostatisticians: Bor-Ming Ou, MS, Thomas J. Tosch, PhD, Arthur Johnson, PhD, Jack Becktel, MS.

Central Research Pharmacy: Chief: Mike Sather, RPh, MS, Marina Chang, RPh, John P. Van Eeckhout, RPh.

Enhanced 24-Hour Norepinephrine and Renin Secretion in Young Patients with Essential Hypertension: Relation with the Circadian Pattern of Arterial Blood Pressure

MICHAEL L. TUCK, MD, NAFTALI STERN, MD, and JAMES R. SOWERS, MD

This study examines the possibility that 24-hour differences in blood pressure (BP) regulation between hypertensive and normotensive subjects is related to changes in 24-hour secretory patterns in circulating pressor hormones. Nine young subjects with normal BP and 9 patients with essential hypertension (EH) were studied during 24-hour recumbency. Every 20 minutes samples were taken to determine plasma norepinephrine (NE) levels and plasma renin activity (PRA). BP was measured every 20 minutes by automatic recording. A distinct circadian rhythm was demonstrated for mean BP, NE and PRA in both groups. Nocturnal reductions in mean BP, NE and PRA related best to the sleep-wakefulness cycle in both groups. Circadian changes in mean BP correlated with NE levels in both normal subjects and patients with EH. The most striking difference between the 2 groups was the absolute levels of mean BP, NE and PRA, which were higher in the EH group at most time points in the 24-cycle. Differences in levels of NE and PRA between the 2 groups were most accentuated during sleep. Thus, young persons with EH show evidence of enhanced sympathetic nervous activity throughout the 24-hour cycle, which is most pronounced during sleep. The multiple sampling approach offers a more sensitive indicator of the role of pressor hormones in BP maintenance.

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Plasma norepinephrine (NE) levels have been reported to be higher in persons with essential hypertension (EH), especially in younger persons, compared with age-matched controls.[1] Most studies used single time-point sampling, and given the considerable variability of plasma NE, only the inclusion of multiple investigations, as reported by Goldstein,[1] allow the analysis of plasma NE to reach significance in younger persons with EH. Using single time-point sampling, a large number of study subjects may be needed to compensate for the effect from factors known to influence NE secretion, such as body weight,[2] caloric intake[2] and dietary sodium.[3] Thus, it remains uncertain whether elevated NE derived by single time-point sampling can serve as an accurate indicator of sustained enhanced sympathetic tone in EH or, rather, reflects increased momentary stress responses. Repeated sampling for plasma NE levels after environmental habituation could provide a more reliable index of basal sympathetic tone. Further, if plasma NE is sampled frequently, coupled with multiple blood pressure (BP) measurements, the relevance of NE to the hour-to-hour control of basal BP can be assessed.

This study examines mean BP levels, plasma NE and plasma renin activity (PRA) sampled every 20 minutes for 24 hours in young persons with normal BP and those with EH. We examined whether maintenance of high BP in young subjects with EH was correlated with basal circulating levels of these pressor hormones as examined over a 24-hour period.

Methods

Subjects: Nine young patients (mean age 29 ± 3 years, range 22 to 46) with EH and 9 young, normotensive control subjects (mean age 24 ± 3 years, range 22 to 39) were studied after they gave informed consent. Patients with EH who were receiving treatment discontinued taking medication 3 weeks before the study. Secondary causes of high BP were excluded by history, physical examination, renal and electrolyte function, urinary metanephrine levels, and hypertensive urographic results. Subjects were hospitalized in a special study ward for 5 days and were studied while receiving a constant 100-mmol sodium and 80-mmol potassium diet with noncaffeinated fluids on request.

From the UCLA School of Medicine, Los Angeles, California, and the Veterans Administration Medical Center, Sepulveda, California. Manuscript received June 1, 1984; revised manuscript received September 4, 1984, accepted September 6, 1984.

Address for reprints: Michael L. Tuck, MD, Veterans Administration Medical Center (111E), 16111 Plummer Street, Sepulveda, California 91343.

Twenty-four-hour recumbency studies: Before the study periods, subjects underwent 24 hours of habituation in a sound-proofed room containing a viewing window, with simulated blood sampling through an indwelling venous catheter and BP monitoring by an Arteriosonde (Hoffman-LaRoche) every 20 minutes. On the fifth day of the constant diet, 24-hour urine samples were collected to measure sodium and potassium levels. The 24-hour recumbency studies were performed on day 6, beginning at 0700 hours, when an indwelling venous catheter was inserted in an antecubital vein. Blood sampling was begun at 0800 hours. The venous catheter was connected to a sampling line passing through a port in the wall and maintained patent by a slow saline drip. Blood samples (2 ml) were collected every 20 minutes to measure NE and PRA levels. BP was monitored by Arteriosonde every 20 minutes. Mean BP was calculated as the diastolic plus one-third of the pulse pressure. Patients remained supine during the study except during meals, when the head of the bed was elevated 30°. The sleep period was 2300 to 0600 hours and meals were at 0800, 1200 and 1800 hours.

Hormone assays: PRA was collected in prechilled tubes and was measured by radioimmunoassay of the angiotensin I generated during 60 minutes of incubation at pH 7.4 and at 37°C.[4] The sensitivity of this assay is 0.2 ng/ml·hour^{-1} and the intraassay coefficient of variation is 5.9%. Samples for NE were collected in prechilled tubes, stored at −100°C and analyzed within 2 weeks. The plasma NE level was measured by the single isotope radioenzymatic method previously described.[3] The sensitivity of this assay is 10 pg/ml with an interassay coefficient of variation of 8 to 12%. Serum and urinary sodium levels were measured by atomic absorption spectrophotometry.

Differences in mean BP and hormonal assays at different times were analyzed using multiple-comparison analysis techniques and the repeated sampling analysis of variance method. Chronobiologic characteristics of mean BP and hormonal measurements during the 24-hour period were determined for each subject by previously described methods.[5]

Results

Patients with EH and control subjects did not differ significantly in mean urinary and sodium levels (122 ± 14 vs 111 ± 16 mmol per 24 hours) after 5 days of diet. They also had similar levels of urinary potassium for the constant potassium intake. Mean serum sodium levels (142 ± 2 mmol/liter) and serum potassium levels (4.2 ± 0.2 mmol/liter) in patients with EH were not significantly different from those in normotensive control subjects. Body weight and mean BP did not change significantly during the dietary equilibration period.

Mean blood pressure: Both groups of subjects demonstrated a reduction in mean BP that best related to the sleep-wakefulness cycle (Fig. 1). Mean BP levels were chosen for representation because they accurately reflected the circadian pattern of both systolic and diastolic blood pressure and correlated best with hormonal circadian patterns. The reduction in mean BP occurred during the first 2 hours of sleep and remained reduced until 30 to 90 minutes before the onset of arousal. The percent reduction in mean BP with sleep from previous waking levels was greater ($p < 0.05$) in the patients with EH (10.2%) than in the control subjects (8.2%). Mean BP increased abruptly in both groups in the early period before awakening and peak levels occurred during early morning. Thereafter, mean BP decreased toward the afternoon, with a moderate surge between 1700 and 2000 hours. The mean fluctuation of mean BP was 25 mm Hg (range 97 to 122) for patients with EH and 18 mm Hg (range 75 to 93) for the control subjects. The lowest mean BP levels in patients with EH occurred later in sleep than it did in the control subjects. Both groups had at least 5 to 6 mean BP peaks (mean BP 15% above mean 24-hour levels), which were most prominent during wakefulness. Absolute levels of mean BP were markedly higher in EH patients at all points during the 24-hour period. The transverse mean for mean BP levels for the patients with EH (110 ± 2.3 mm Hg) was greater ($p < 0.01$) than that for the normotensive control subjects (82 ± 4.7 mm Hg).

Norepinephrine: Reductions in NE during the 24-hour cycle best related to sleep periods, although

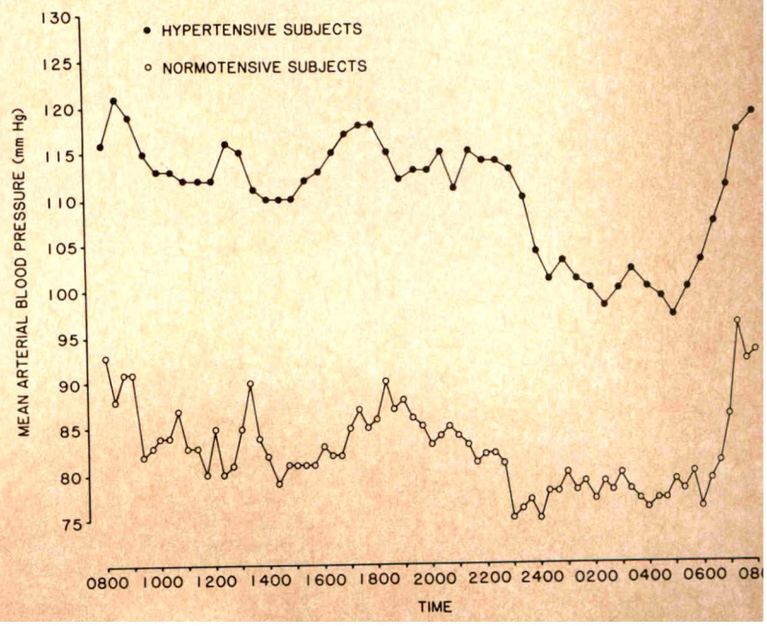

FIGURE 1. Mean values for recumbent levels of mean arterial blood pressure over a 24-hour period in normotensive control subjects and patients with essential hypertension. The sleep period was from 2300 to 0600 hours.

mean levels also slowly decreased throughout the waking hours in both groups (Fig. 2). In the normotensive control subjects there was a 33% reduction in levels between 0400 to 0600 hours, when values were reduced 58% from peak levels at 0920 hours. Arousal (0600 to 0700 hours) was accompanied by an abrupt 25 to 33% increase in NE in both groups. Individual analysis of NE curves in both groups revealed 5 to 6 secretory peaks (NE, 25% above the mean 24-hour concentration), usually occurring between 0600 and 1800 hours. Absolute levels of NE were significantly higher in patients with EH at most of the sampling times during the 24-hour period; the most marked difference occurred during the latter part of sleep (Fig. 2). The transverse mean NE in patients with EH (274 ± 5.9 pg/ml) was significantly ($p < 0.01$) greater than that in the control subjects (237 ± 6.6 pg/ml). Circadian changes in mean BP were highly correlated with plasma NE in the control subjects ($r = 0.62$; $p < 0.01$) and patients with EH ($r = 0.67$; $p < 0.01$).

Renin: PRA decreased in the early evening (1800 to 2300 hours) and began to slowly increase after 1 to 3 hours sleep, reaching the highest levels during the second half of sleep in both groups (Fig. 3). These changes were much less pronounced and consistent in the EH group compared with the control group. During the day there were no significant differences between PRA in either group. The number of secretory peaks for PRA (PRA, 25% above the mean 24-hour concentration) analyzed individually was 6 to 8 peaks for both groups. Although PRA was higher in EH subjects during the 24-hour period these differences reached statistical significance consistently only during sleep. The transverse mean PRA, however, was greater ($p < 0.05$) in the EH group (2.3 ± 0.6 ng/ml·hour^{-1}) than in the control group (1.3 ± 0.4 ng/ml·hour^{-1}). Correlations between 24-hour changes in PRA with NE and mean BP were not significant in either group.

Discussion

The results are consistent with previous reports that patients with EH, like normotensive persons, retain a distinct circadian rhythm of mean BP that best fits the sleep-wakefulness cycle.[6–8] However, mean BP values were significantly higher at all points in the 24-hour cycle in patients with EH. Thus, EH subjects, although they have a greater amplitude of mean BP, show a circadian rhythm of BP similar to that of normotensive

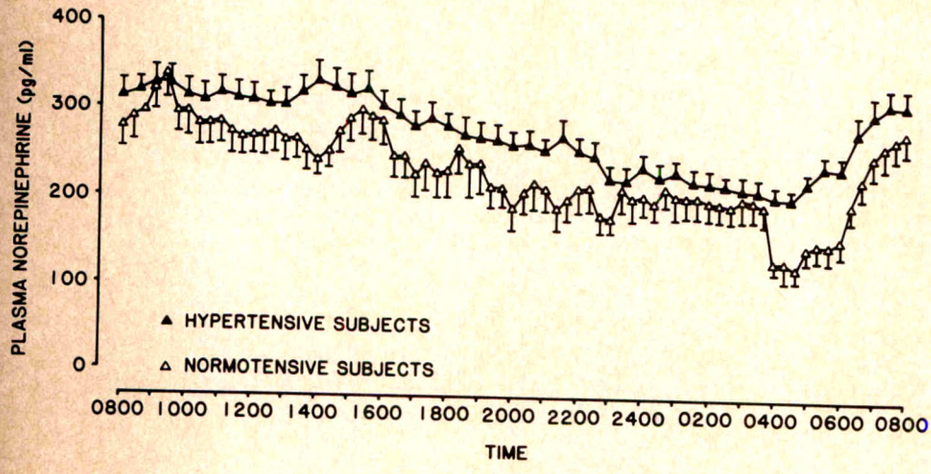

FIGURE 2. Plasma norepinephrine levels during recumbency over a 24-hour period in normotensive control subjects and patients with essential hypertension. Values are mean ± standard error of the mean.

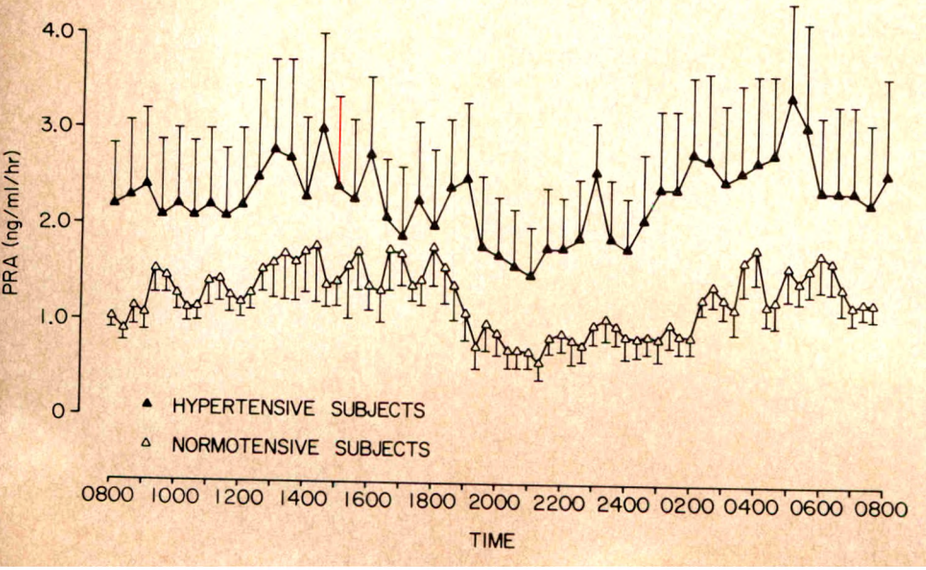

FIGURE 3. Levels of plasma renin activity (PRA) during recumbency over a 24-hour period in normotensive control subjects and patients with essential hypertension. Values are mean ± standard error of the mean.

persons. BP decreases during sleep in normal humans and also decreases in persons with EH, averaging 10 to 12% in both groups.[6–8] Home monitoring of BP in patients with EH shows an even greater sleep-related reduction in BP, and one cannot exclude some dampening effect on BP variation on admission of subjects to a metabolic study unit. A distinct absence of sleep-related reductions in BP was noted in malignant hypertension[8] and pheochromocytoma,[9] suggesting that changes in PRA and NE contribute to diurnal changes in BP.

Our study subjects had distinct circadian rhythms of NE; NE levels were highest in the early morning and decreased during the day, followed by a more pronounced, sleep-related nocturnal decrease during the initial hours of sleep in both groups. However, both patients with EH and control subjects failed to demonstrate a further reduction during the later hours of sleep. Mean NE levels were high in the EH group throughout the 24-hour study period, and the differences between the EH group and the control group were significant at about 50% of the time points sampled throughout the 24-hour cycle. These observations confirm and add the dimension of time to studies using single time-point sampling that have reported elevated NE in young EH subjects.[1,10] Thus, the multiple sampling techniques may offer a more sensitive index of the relation between sympathetic nervous system activity and control of BP.

In 2 previous reports 24-hour NE levels were assessed in patients with EH. Liebau and Manitius[11] found no difference between EH and control subjects in NE levels in the morning and evening, a period hardly sufficient for representation of the 24-hour activity of the sympathetic nervous system. Zadik et al[12] could not find differences in integrated 24-hour NE levels determined by continuous sampling in ambulant subjects with EH. This study incorporated a higher sodium intake (200 mEq/24 hours), a wider age range of subjects (8.5 to 61 years) and a racial population different from that in our study. The higher 24-hour NE levels in our patients with EH may not be pertinent to the general EH population, but should be viewed as representative of a younger group with perhaps a shorter duration of EH.

The enhanced sympathetic tone in younger patients with EH may be a factor to their higher 24-hour BP values. However, caution must be applied in inferring a cause-effect relation or biologic significance from the study. The differences in NE levels between EH and control subjects may not be of sufficient magnitude to alter BP. Infusion studies of NE in man to create increments in NE in the 30- to 60-pg/ml range have not altered BP.[13] These were short-term studies, however, that may not reflect a longer-term influence of NE on BP regulation. Cardiovascular variables that may reflect increased sympathetic nervous system activity, such as pulse rate, were not monitored at 20-minute intervals in this study. Baseline pulse rate, however, was higher in patients with EH than in control subjects.

A diurnal rhythm of PRA was present in our control subjects, with highest values between 0200 and 0800 hours and lowest values from 1800 hours through the first part of sleep. The circadian rhythm of PRA has control mechanisms of renin release, including sodium-volume homeostasis and BP.[14–16] Circadian periodicity of PRA may best relate to the central nervous system's control of renin release as β-adrenergic blockade abolished the nocturnal increase in PRA.[17] Our patients with EH had a circadian pattern of PRA similar to that of the control subjects, but a much greater variance in PRA values existed between individual time points. EH patients also had higher mean PRA levels compared with control subjects throughout most of the 24-hour period. Two of the 9 patients with EH did, however, have circadian PRA values that were indistinguishable from those of the control subjects, suggesting that with a larger population of persons with EH, distinct subgroups of PRA periodicity may emerge. The enhanced 24-hour sympathetic tone in most of our patients with EH may explain the high PRA levels. The release of renin is influenced by sympathetic outflow[18] and a positive correlation between NE and PRA has been shown in several studies in patients with EH.[19,20] Although PRA did not correlate with NE or mean BP in our patients, a contributory role for the higher PRA levels in modulation of higher vascular tone in those with EH cannot be excluded.

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Role of Prostaglandins in the Renal Handling of a Salt Load in Essential Hypertension

BRUNO TRIMARCO, MD, ANTONIO DE SIMONE, MD, ALBERTO CUOCOLO, MD, BRUNO RICCIARDELLI, MD, MASSIMO VOLPE, MD, PAOLA PATRIGNANI, MD, LUIGI SACCÀ, MD and MARIO CONDORELLI, MD

Renal function and systemic hemodynamics were assessed in 10 hypertensive patients and in 10 age-matched normotensive subjects during control conditions (80 mEq of sodium/day) and after a salt load, either alone (480 mEq/day) or combined with indomethacin or sulindac. Indomethacin was used to induce ubiquitous inhibition of prostaglandin synthesis and sulindac to inhibit prostaglandin synthesis in all tissues except the kidney. Under control conditions there was no significant difference between the 2 groups in any measurement except blood pressure and total peripheral resistance. Also, the changes induced by salt load in the 2 groups were comparable. However, after indomethacin administration, only hypertensive patients showed a significant reduction in the 24-hour sodium excretion (from 417 ± 61 to 317 ± 49 mEq, $p < 0.05$), so that the difference between this value and the corresponding value of normotensive subjects (453 ± 79 mEq) became significant ($p < 0.05$). The changes in sodium excretion in hypertensive patients were significantly correlated with the changes in renal plasma flow ($r = 0.803$, $p < 0.01$). However, cardiac output and renal blood flow showed a similar pattern in normal and hypertensive persons. Finally, after the addition of sulindac to salt load, the differences in the 24-hour sodium excretion vanished. These results were also confirmed in an ancillary study performed, using the same protocol, in 10 other hypertensive patients using ibuprofen rather than indomethacin. Our data suggest that renal prostaglandins participate in renal disposal of chronic salt load in hypertensive patients but not in normal persons. (Am J Cardiol 1985; 55:116–121)

Although the natriuretic response to a sodium load in patients with essential hypertension changes throughout life, the variability of this response has not been explained. Prostaglandins are gaining recognition as important modulators of hemodynamic and excretory function in the mammalian kidney.[1–3] Therefore, in the present study we investigated the role of renal and extrarenal prostaglandins in the handling of a sodium load by the kidney in patients with established hypertension. For this purpose, we assessed in normal subjects and in hypertensive patients the effects of indomethacin and sulindac on sodium and potassium excretion, urine output and renal and systemic hemodynamics. Both indomethacin and sulindac are inhibitors of prostaglandin synthesis. However, indomethacin has a diffuse action, whereas sulindac has been reported to possess a sparing effect on prostaglandin synthesis in the kidney,[4,5] probably due to the absence of the active form of the drug in this organ. Because indomethacin induces vasoconstriction independent of its effect on fatty acid cyclooxygenase,[6] we repeated the study in another group of hypertensive patients using ibuprofen in order to clarify whether the results observed with indomethacin were entirely to be ascribed to prostaglandin synthesis inhibition.

From the Istituto di Clinica Medica I, II Facoltá di Medicina, Universitá di Napoli, Napoli, Italy, and the Istituto di Farmacologia, Facoltá di Medicina, Universitá Cattolica di Roma, Roma, Italy. This study was supported in part by CNR Grant 83.02087.04, Rome, Italy. Manuscript received May 23, 1984; revised manuscript received September 11, 1984, accepted September 13, 1984.

Address for reprints: Bruno Trimarco, MD, Istituto di Clinica Medica I, II Facoltá di Medicina, Via S. Pansini 5, 80131 Napoli, Italy.

Methods

Subjects and procedures: The study was carried out in 20 volunteers (15 men, 5 women). Ten were patients with mild essential hypertension. They were 17 to 56 years old (mean age 32 ± 2). Their mean body weight was 72 ± 3 kg. All had an average supine diastolic blood pressure (BP), measured on 4 occasions at least 1 week apart, of 95 to 110 mm Hg. The other 10 volunteers were normal subjects and constituted the control group. They were 18 to 54 years old (mean age 30 ± 4). Their mean body weight was 72 ± 2 kg. Secondary forms of hyper-

TABLE I Humoral and Hemodynamic Measurements Recorded in Control Conditions and During Salt Load, Alone or Associated with Either Indomethacin or Sulindac Administration

	Sodium Intake (mEq/day)	GFR (ml/min)	PRAs (ng/ml/hour)	PRAu (ng/ml/hour)	ALDs (pg/ml)	ALDu (pg/ml)	SAP (mm Hg)	DAP (mm Hg)	HR (beats/min)	Hct (%)
A	80	100 ± 5	1 ± 0.2	2.8 ± 0.9	77 ± 3	148 ± 5	123 ± 6	82 ± 3	73 ± 4	45 ± 1
B		100 ± 8	1.6 ± 0.2	3.4 ± 0.5	104 ± 14	181 ± 27	156 ± 10‖	102 ± 2¶	76 ± 4	45 ± 2
A	480	124 ± 8	0.3 ± 0.1†	0.6 ± 0.2†	45 ± 8†	61 ± 9†	130 ± 3	83 ± 5	71 ± 4	46 ± 1
B		115 ± 10	0.3 ± 0.2†	0.6 ± 0.1†	68 ± 13†	82 ± 11†	166 ± 12‖	108 ± 3¶	70 ± 3	45 ± 2
A	480 + I	116 ± 15	0.3 ± 0.2†	0.3 ± 0.2†	45 ± 8†	48 ± 8†	127 ± 3	84 ± 4	70 ± 5	44 ± 3
B		101 ± 14	0.2 ± 0.1†	0.6 ± 0.2†	70 ± 8†	91 ± 16†	173 ± 11*‡‖	114 ± 4*‡¶	63 ± 2	44 ± 3
A	480 + S	124 ± 15	0.5 ± 0.2†	0.5 ± 0.2†	41 ± 2†	58 ± 8†	128 ± 3	85 ± 2	67 ± 6	45 ± 1
B		114 ± 2	0.2 ± 0.1†	0.6 ± 0.2†	64 ± 11†	94 ± 19†	166 ± 10§‖	109 ± 2§¶	68 ± 2	43 ± 2

Each value represents mean ± standard error of the mean; n = 10.

Different from the corresponding value in the same group with 80-mEq/day sodium diet:* $p < 0.05$, † $p < 0.01$; ‡ different from the corresponding value in the same group with 480-mEq/day sodium diet: $p < 0.05$; § different from the corresponding value in the same group with 480-mEq/day sodium diet + I: $p < 0.05$; * different from the corresponding value in normotensive subjects, ‖ $p < 0.05$ and ¶ $p < 0.01$.

A = normotensive subjects; ALDs = plasma aldosterone concentration supine; ALDu = plasma aldosterone concentration upright; B = hypertensive patients; DAP = diastolic arterial pressure; GFR = glomerular filtration rate; Hct = hematocrit; HR = heart rate; I = indomethacin; PRAs = plasma renin activity supine; PRAu = plasma renin activity upright; S = sulindac; SAP = systolic arterial pressure.

tension were ruled out on the basis of the history, physical examination and routine screening tests. Patients with major diseases other than hypertension were excluded from the study. BP was measured with subjects in the supine position on a comfortable bed and according to the recommendations of the American Heart Association.[7] No patient had been taking any drug for at least 2 weeks before the study was begun. Subjects were asked not to take any other medications during the course of the study and to fast and abstain from fluid for 12 hours before the study. In the week preceding the study as well as throughout the study, each subject was given a diet containing 80 mEq/day of sodium and 70 mEq/day of potassium. Personal food preferences were followed as closely as possible.

The subjects were initially studied under control conditions. On the day before the test, the 24-hour urine samples were collected and 3 blood samples were drawn 12 hours apart in order to measure 24-hour urine output, urinary sodium and potassium excretion and glomerular filtration rate (GFR) as creatinine clearance. On the day of testing procedure, at 9 AM, BP and heart rate were recorded after 15 minutes of recumbency; an M-mode echocardiogram was also performed to estimate cardiac output. Renal plasma flow (RPF) was then determined as p-aminohyppurate clearance as previously described.[8] Furthermore, plasma renin activity and aldosterone concentration were measured in the supine position and after 2 hours in the upright position. Then, the daily diet was supplemented with 4 doses of 100 mmol of cristalline sodium chloride wrapped by wafer to yield a total amount of 480 mEq/day of sodium intake. On the fifth day of high sodium intake, all measurements were repeated. Then, all subjects received either indomethacin or sulindac in a randomized fashion for 3 days (orally administered indomethacin, 50 mg twice on the first day, 50 mg 3 times on the second day and 50 mg 2 hours before starting the procedure on the third day; orally administered sulindac, 200 mg twice on the first day, 200 mg 3 times on the second day and 200 mg 2 hours before starting the testing procedure on the third day). A short treatment period was used because of the possible attenuation of the inhibitory effect on prostaglandin synthesis despite sustained drug administration.[9] After 8 days of high sodium intake, all measurements were repeated. Finally, after a 2-day washout period (ninth and tenth days), the subjects received the other pharmacologic treatment (indomethacin or sulindac; eleventh, twelfth and thirteenth day) and measurements were again repeated on the thirteenth day of high sodium intake. The administered inhibitor was known only to the trial coordinator and measurements were observer-blind. The adequacy of prostaglandin synthesis inhibition induced by the different pharmacologic treatments was assessed through radioimmunoassay of serum thromboxane (Tx) B_2, which reflects thrombin-induced activation of platelet TxA_2 production during whole blood clotting.[10]

Study with ibuprofen: The study was carried out in 10 additional patients (6 men, 4 women) with mild essential hypertension as previously defined. They were 20 to 49 years old (mean 33 ± 2) and had a mean body weight of 74 ± 5 kg. They were asked to follow the same guidelines pertaining to diet, personal habits and drug intake as patients in the other 2 groups. The subjects were initially studied under control conditions. The same procedures were followed as in the previous 2 studies, both on the test days and on the days before testing procedures. Then, the daily diet was supplemented with sodium chloride as already described and each subject was studied again on the fifth day of high sodium intake. Finally, ibuprofen was administered orally for a 3-day period (400 mg twice on the first day, 400 mg 3 times on the second day and 400 mg 2 hours before starting the test procedure on the third day), and all measurements were repeated on the eighth day of high sodium intake.

Analyses: Plasma renin activity was measured according to the method described by Menard and Catt[11] (sensitivity 5 ± 0.4 pg/tube Ang. I, i.e., plasma renin activity 0.06 ng/ml/hour) and plasma aldosterone concentration according to the method described by McKenzie and Clements[12] (sensitivity 6 ± 1 pg/ml). M-mode echocardiography was performed as previously described.[13] The tracings were coded and read by 2 observers in a double-blind fashion.

Either 1-way or 2-way analysis of variance was used as appropriate. Data are expressed as mean ± standard error of the mean.

Results

As expected, during control conditions hypertensive patients showed only BP and total peripheral resistance (TPR) higher than normotensive subjects (Table I, Fig. 1 and 2). In normotensive subjects, high sodium intake induced a significant increase in cardiac output and in RPF (Fig. 1) as well as in the 24-hour urine output and sodium excretion (Fig. 2). BP and heart rate did not change significantly (Table I). Plasma renin activity and aldosterone concentrations, both supine and upright, decreased significantly (Table I), while the changes in

24-hour urinary potassium excretion and GFR were not statistically significant (Fig. 2, Table I). In hypertensive patients, high sodium intake induced changes similar in magnitude to those observed in normal subjects, so that the differences between the 2 groups were the same as those found under control conditions (Table I, Fig. 1). The effects of indomethacin and sulindac on the responses to high sodium intake were not affected by the sequence of drug administration. Therefore, the results obtained when indomethacin was used as the first treatment (eighth day study) were pooled with those obtained when the same drug was used as the second treatment (thirteenth day). Also, the data pertaining to sulindac administration were pooled. Platelet cyclooxygenase activity was inhibited by more than 90% after each of the 2 treatments.

In normal subjects, none of the considered variables changed significantly when indomethacin was added to high sodium intake (Table I, Fig. 1 and 2). However, the significant increase in cardiac output and RPF induced by sodium load alone was lost after indomethacin administration. In hypertensive patients, indomethacin induced a significant increase in BP compared with either of the 2 previous stages of the protocol (Table I). This increase in BP apparently results from a sharp increase in TPR, which became significantly higher than the TPR in the previous stages. Cardiac output significantly decreased from the values found during the high sodium intake alone, and it was no longer different from the control values. Also, RPF decreased in 8 of 10 patients compared with values during high sodium intake alone, although the mean decrease did not reach statistical significance. These hemodynamic changes were accompanied by a significant reduction in the 24-hour urine excretion. In hypertensive patients, but not in normotensive subjects, a significant correlation was found between the changes in RPF and those in sodium excretion induced by indomethacin administration during high sodium intake ($r = 0.803$, $p < 0.01$). Finally, in normal subjects the addition of sulindac to high-sodium diet induced changes similar to those observed with indomethacin (Fig. 1).

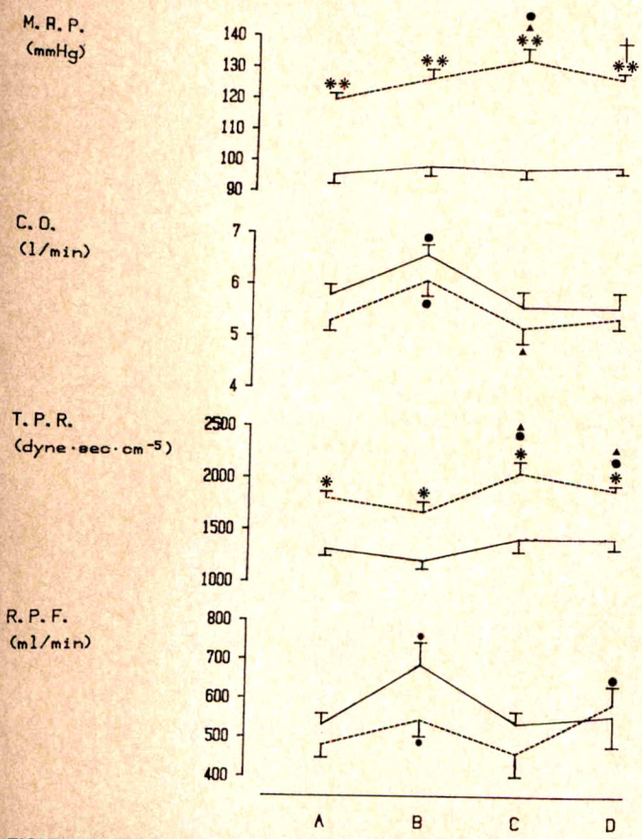

FIGURE 1. Mean arterial pressure (M.A.P.), cardiac output (C.O.), total peripheral resistance (T.P.R.) and renal plasma flow (R.P.F.) under control conditions (**A**) and during salt load, alone (**B**) or associated with indomethacin (**C**) or sulindac (**D**) in normal subjects (**continuous line**) and in hypertensive patients (**dotted line**). Each **point** represents the mean ± standard error of the mean; n = 10. Different from the corresponding value obtained in normal subjects: * $p < 0.05$ and ** $p < 0.01$; ● different from the corresponding value in the same group in control conditions (80-mEq/day sodium diet) ($p < 0.05$); ▲ different from the corresponding value in the same group with 480-mEq/day sodium diet: $p < 0.05$; † different from the corresponding value in the same group with 480-mEq/day sodium diet plus indomethacin: $p < 0.05$.

In contrast, in hypertensive patients the administration of sulindac during the high-sodium diet induced changes different from those observed with indomethacin. In particular, we did not observe the significant increase in BP found during indomethacin treatment. Furthermore, the increase in TPR and the decrease in cardiac output were less marked. During sulindac treatment, hypertensive patients, as a group, showed higher RPFs than in previous stages of our protocol. The mean RPF in hypertensive patients during high sodium intake was similar to that found when sulindac was added. In both stages, RPF was higher than the mean value found during low sodium intake as well as during indomethacin administration. However, probably because of the heterogeneous response of the individual patients, no significant difference was reached when indomethacin was compared with sulindac. On the other hand, statistical significance was reached when comparing the percentage of cardiac output delivered to the kidney in these 2 stages of our study (15 ± 4% vs 25 ± 2%, $p < 0.05$). Furthermore, the ratio of RPF to cardiac output became significantly higher when sulindac was added to the high sodium intake also as compared with the high sodium intake alone (25 ± 2% vs 20 ± 2%, $p < 0.05$). In addition, the reduction in the 24-hour urinary sodium excretion observed after sulindac treatment was less marked than that found after indomethacin. Therefore, this response can not be differentiated either from that observed in the same group of patients during high sodium intake alone or from that observed in normal subjects during sulindac administration (Fig. 2).

Study with ibuprofen: Under control conditions, no significant difference was detectable in all the considered parameters between the hypertensive patients enrolled in this study (Table II, Fig. 3) and those participating in the study previously described. In the ibuprofen study, the high sodium intake alone elicited changes in the measurements similar to those observed both in normotensive and in hypertensive subjects in the previous study (Table II, Fig. 3). Furthermore, addition of ibuprofen to the sodium load induced changes

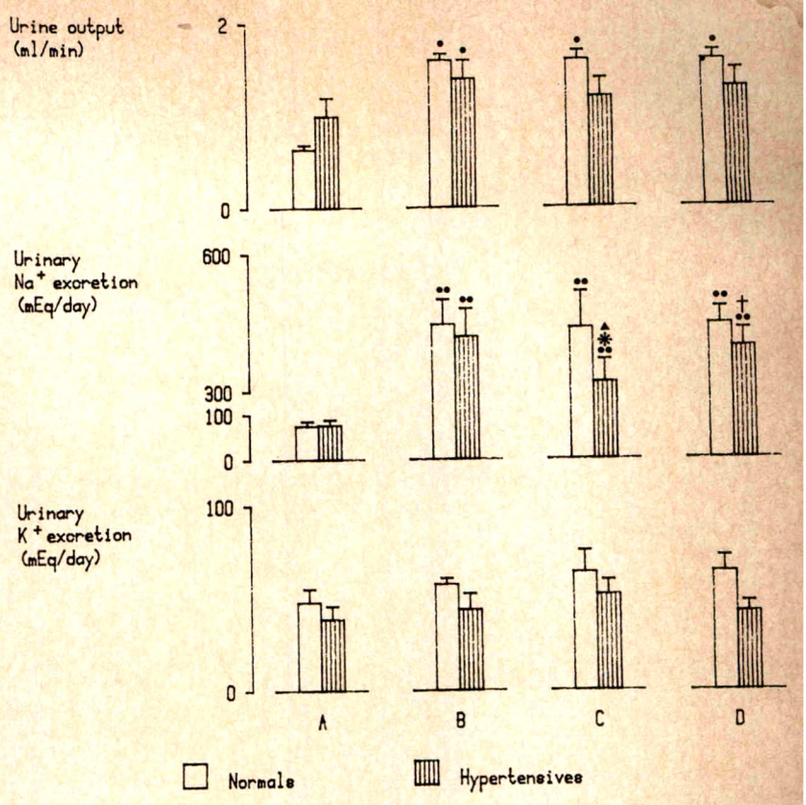

FIGURE 2. Twenty-four-hour urine output and urinary sodium and potassium excretion in control conditions (**A**) and during salt load, alone (**B**) or associated with indomethacin (**C**) or sulindac (**D**) in normotensive subjects and in hypertensive patients. Each **bar** represents mean ± standard error of the mean, n = 10. Statistical analysis as in Figure 1. Different from the corresponding value in the same group in control conditions (80-mEq/day sodium diet: ● $p < 0.05$ and ● ● $p < 0.01$). Other symbols as in Figure 1.

in hemodynamics similar to those previously observed in hypertensive patients treated with indomethacin (Table II) and a significant reduction in the 24-hour urine output and urinary sodium excretion (Fig. 3).

Discussion

Two experimental approaches are available in order to investigate the possibility that endogenous prostaglandins participate in pathophysiological phenomena: prostaglandin assay in blood, urine or tissue specimens, and administration of drugs that inhibit prostaglandin synthesis. Measurement of prostaglandin concentration may provide more complete information about the role of these substances, because it indicates both the specific prostaglandin involved and the degree of the evoked change in their concentration. However, the reproducibility and the sensitivity of prostaglandin assay are limited by several factors.[3,14] Furthermore, it remains uncertain whether an observed change in prostaglandin levels represents a cause or merely a consequence of a given phenomenon. Given the above limitations of prostaglandin assay, in this study we chose the use of prostaglandin synthesis inhibitors to test the hypothesis that prostaglandins play a role in renal sodium handling in essential hypertension. In particular, we used indomethacin and sulindac in an attempt to investigate the relative roles of renal and extrarenal prostaglandins in the renal handling of a salt load. Because we could duplicate the results obtained using indomethacin with ibuprofen, it appears reasonable to ascribe the changes observed in our patients with

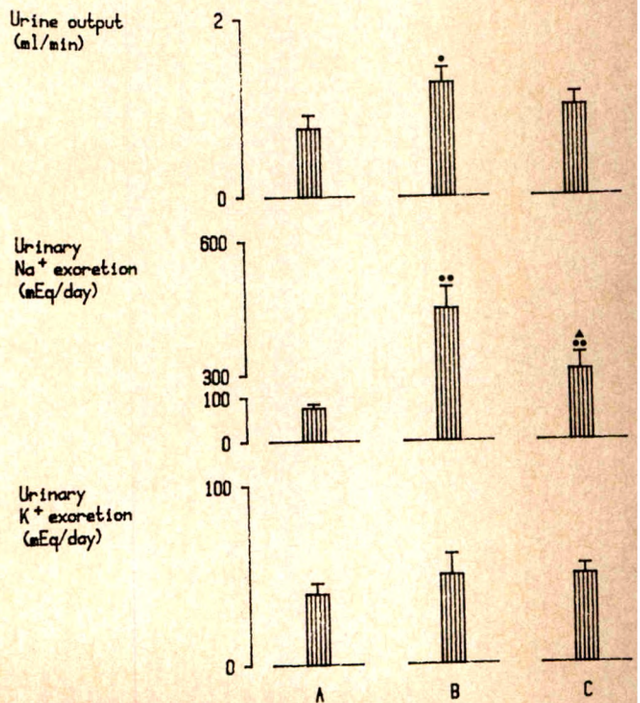

FIGURE 3. Twenty-four-hour urine output, urinary sodium and potassium excretion in control conditions (**A**) and during salt load, alone (**B**) or associated with ibuprofen (**C**). Each **bar** represents mean ± standard error of the mean; n = 10. Different from the corresponding value in the same group in control conditions (80-mEq/day sodium diet): ● $p < 0.05$ and ● ● $p < 0.01$; ▲ different from the corresponding value in the same group with 480-mEq/day sodium diet: $p < 0.05$.

TABLE II Humoral and Hemodynamic Measurements Recorded in Hypertensive Patients in the Basal State (80-mEq/day Sodium Diet) (A) and During Salt Load (480-mEq/day Sodium Diet) Alone (B) or Associated with Ibuprofen (C)

	RPF (ml/min)	GFR (ml/min)	PRAs (ng/ml/h)	PRAu (ng/ml/h)	ALDs (pg/ml)	ALDu (pg/ml)	SAP (mm Hg)	DAP (mm Hg)	HR (beats/min)	CO (l/min)	TPR (dynes s cm^{-5})	Hct (%)
A	508 ± 24	98 ± 8	1.4 ± 0.3	3.3 ± 0.8	117 ± 16	174 ± 19	156 ± 10	104 ± 7	81 ± 2	5.5 ± .2	1766 ± 69	44 ± 1
B	570 ± 51*	116 ± 15	0.2 ± 0.1†	0.6 ± 0.1†	60 ± 9†	78 ± 13†	164 ± 8	108 ± 3	76 ± 2	6.2 ± .3*	1689 ± 121	46 ± 1
C	483 ± 51	104 ± 11	0.2 ± 0.2†	0.5 ± 0.3†	64 ± 11†	79 ± 18†	176 ± 10*‡	119 ± 7	79 ± 5	5.6 ± .5	2100 ± 117*‡	43 ± 4

Each value represents mean ± standard error of the mean; n = 10.
Different from the corresponding value obtained during 80-mEq/day sodium diet: * $p < 0.05$ and † $p < 0.01$; ‡ different from the corresponding value obtained during 480-mEq/day sodium diet, $p < 0.05$.
CO = cardiac output; RPF = renal plasma flow; TPR = total peripheral resistance; other abbreviations as in Table I.

the above drugs to concurrent changes in prostaglandin synthesis rather than to nonspecific pharmacologic properties of these drugs independent of prostaglandin synthesis. Finally, the possibility of incomplete prostaglandin synthesis inhibition is unlikely because our data from TxB_2 assay show that a sufficient inhibition of cyclooxygenase activity was achieved in our patients.

In our study, an increased sodium intake elicited similar changes in hemodynamics and renal function both in normal and hypertensive subjects. In particular, in agreement with a previous study,[15] the response of cardiac output and urinary sodium excretion was comparable in the 2 groups. In contrast, when prostaglandin synthesis inhibitors were added to the high sodium diet, hypertensive patients responded differently from normotensive subjects. After indomethacin or ibuprofen treatment, the 24-hour renal sodium excretion sharply decreased and BP increased in hypertensive but not in normotensive subjects. In contrast, after addition of sulindac to the sodium load, we observed in hypertensive patients a 24-hour sodium excretion level comparable to that of normal subjects. These observations indicate that the prostaglandin system plays a role in favoring the renal disposal of a chronic sodium load in hypertensive patients but not in normotensive subjects, and suggest that renal prostaglandins are mainly responsible for this phenomenon. Furthermore, the lack of significant changes in BP in hypertensive patients during sulindac administration suggests that the increase in BP observed during indomethacin administration is due to the reduced sodium excretion rather than to the direct effect of indomethacin or ibuprofen on prostaglandin control of vascular tone, as described by previous investigators.[16] Finally, our data do not reveal the mechanism underlying the impairment of the renal handling of a salt load during indomethacin administration. Our study shows that both indomethacin and ibuprofen normalized the increased RPF induced by the high sodium intake, in both normotensive and in hypertensive subjects, although only hypertensive patients showed a concurrent reduction in sodium excretion. Thus, in normal subjects the kidney maintains a normal rate of sodium excretion even in the face of a reduced RPF after inhibition of prostaglandin synthesis. This indicates that the increase of the RPF after a sodium load is not a prerequisite for the enhanced renal excretion of sodium to occur. In hypertensive patients, on the other hand, the simultaneous reduction of both RPF and sodium excretion makes it impossible to ascertain whether the 2 phenomena are independent or linked by a cause-effect relation. The existence of a significant direct correlation between sodium excretion and RPF after indomethacin in hypertensive patients indirectly supports the latter interpretation. However, renal vasodilatation is only 1 mechanism of prostaglandin-mediated natriuresis. It has been reported that prostaglandin E_2 augments natriuresis in the canine kidney, that is maximally vasodilatated with acetylcholine.[17] Furthermore, in vitro studies have shown that prostaglandins can influence

transepithelial transport of ions both in the thick ascending limb of Henle's loop and in the collecting tube.[18–20] Finally, the observation that during both indomethacin and ibuprofen treatments, but not during sulindac administration, there was a reduction in GFR indicates that also a reduction in the filtered load of sodium may represent an alternative mechanism for the reduced natriuresis after inhibition of renal cyclooxygenase.

The possibility that prostaglandins improve renal function also by mechanisms not involving changes in RPF may offer some advantages in a tentative explanation of the data observed in established hypertensives. Bianchi et al[21] found in normotensive subjects who were first-degree relatives of essential hypertensive persons an RPF higher than that in age-matched normal subjects, and hypothesized that this may represent a compensatory mechanism for a primary, still unidentified, kidney defect in such subjects who are at an increased risk of essential hypertension. In similar subjects, Grim et al[22] demonstrated a blunted natriuretic response to salt load. Therefore, it appears unlikely that an increased RPF, which fails to normalize the natriuretic response in the young subjects, could succeed in older patients with probable vascular changes secondary to long-lasting hypertension. Whatever the case, the observation that the inhibition of renal prostaglandin synthesis impairs sodium excretion in hypertensive patients suggests that prostaglandins exert a pivotal role in renal sodium handling in these patients also in physiologic conditions, i.e., during salt load in which their inhibition has no effect on sodium excretion in normal subjects.

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Immediate Converting-Enzyme Inhibition with Intravenous Enalapril in Chronic Congestive Heart Failure

SPENCER H. KUBO, MD, ROBERT J. CODY, MD, JOHN H. LARAGH, MD, XAVIER E. PRIDA, MD, STEVEN A. ATLAS, MD, ZHUNG YUAN, MD, and JEAN E. SEALEY, DSc

To test the hypothesis that intravenous enalapril is a useful pharmacologic probe of the renin angiotensin system, intravenous enalapril was administered to 9 patients with severe congestive heart failure (CHF). This produced abrupt and complete blockade of converting enzyme, with peak effect occurring at 30 minutes, as reflected by increases of plasma renin activity (from 16.8 ± 6 to 86.6 ± 23 ng/ml/hour) and decreases of plasma aldosterone levels (from 46 ± 14 to 25 ± 6 ng%) (both $p < 0.05$). With reduction of angiotensin II–mediated vasoconstriction, systemic vascular resistance decreased markedly (from 1,974 ± 233 to 1,400 ± 136 dyne s cm^{-5}) and cardiac index was improved (from 1.88 ± 0.9 to 2.20 ± 0.21 liters/min/m^2) (both $p < 0.05$). The time course of angiotensin II levels suggested that the lack of a cumulative effect from additive doses of intravenous enalapril was a reflection of complete inhibition of converting enzyme. One patient did not respond to enalapril; despite comparable hemodynamic severity of CHF, the renin-angiotensin system was not activated in this patient. Thus, intravenous enalapril is capable of rapid and complete inhibition of converting enzyme for the accurate assessment of angiotensin II–mediated vasoconstriction in patients with severe CHF.

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Despite the large number of drugs that induce vasodilatation in congestive heart failure (CHF), those that act by more readily defined mechanisms may also clarify pathophysiology and ultimately lead to more specific therapy.[1,2] One important vasoconstrictor mechanism in severe CHF is activation of the renin-angiotensin system,[3–5] mediated by the potent vasoconstriction of angiotensin II and the sodium and water retention of aldosterone. However, angiotensin and aldosterone are not uniformly stimulated in all patients with CHF.[4] The converting-enzyme inhibitor captopril has been a useful pharmacologic probe to determine the extent of this activity.[6,7] However, the peak effect and completeness of converting-enzyme inhibition are difficult to assess accurately with an orally administered agent. A second-generation converting enzyme inhibitor, enalapril (MK-421), may be another useful probe; however, enalapril is a pro-drug that must be de-esterified with a delayed peak effect of 6 to 8 hours.[8,9] These limitations may be avoided with the intravenous administration of an active drug. In the present study, we characterize the hemodynamic and neurohormonal responses to intravenous enalapril (MK-422) in patients with severe CHF, to assess the usefulness of intravenous enalapril as a pharmacologic probe of the renin-angiotensin system and to determine the degree to which the renin-angiotensin system can be abruptly and completely suppressed.

From the Cardiology Division, Department of Medicine and Pharmacology, The New York Hospital–Cornell University Medical Center, New York, New York. This study was supported in part by General CRC Grant RR-47 from the National Institutes of Health, Bethesda, Maryland. Manuscript received June 1, 1984; revised manuscript received September 5, 1984, accepted September 6, 1984.

Address for reprints: Robert J. Cody, MD, Cardiology Division, Section J-3, New York Hospital–Cornell University Medical Center, 525 East 68th Street, New York, New York 10021.

Methods

The study consisted of 9 patients (7 men, 2 women, aged 38 to 73 years, mean 58) with severe, chronic CHF (New York Heart Association class III or IV) refractory to digitalis and diuretic drugs. Four patients had coronary heart disease (ischemic cardiomyopathy) and 5 had idiopathic cardiomyopathy. No patient had systemic hypertension or recent myocardial infarction and all were clinically stable at the time of the study. The patients were admitted to the Clinical Research Center and placed on a 100-mEq sodium diet. All previous vasodilator therapy was discontinued for at least 4

days. Because of the severity of CHF, digoxin and diuretic drugs were continued at constant doses, although neither was administered on the day of the invasive hemodynamic study.

Hemodynamic study: After an overnight fast, a triple-lumen thermodilution catheter was placed under fluoroscopic guidance. Right atrial and pulmonary capillary wedge pressures were recorded continuously. Thermodilution cardiac output was determined in triplicate and expressed as cardiac index, corrected for body surface area. Arterial blood pressure was continuously recorded after a cannula was placed in a radial artery. Heart rate was monitored from a precordial electrocardiographic lead. Systemic vascular resistance and stroke volume index were calculated from standard formulas.[10]

Patients were allowed to rest for 45 minutes between catheter insertion and baseline hemodynamic determinations and blood sampling to measure plasma renin activity, aldosterone, norepinephrine and angiotensin II levels. A second control measurement was obtained after 30 minutes to ensure stable baseline values.

Patients were given 2 doses of intravenous enalapril to assess its cumulative effect. Based on preliminary data, we administered 1.25 mg as the first dose, followed by 2.5 mg. Because of marked hypotension in the first patient given this regimen, the dosing schedule was changed to 0.625 mg and 1.25 mg for all subsequent patients. After the first dose, hemodynamic values and blood samples to measure plasma renin activity, aldosterone, norepinephrine and angiotensin II levels were taken every 15 minutes for 60 minutes, and then at 90 minutes. Measurements were taken every 30 minutes for 90 minutes after the second dose. Eight patients showed a greater than 15% decrease of systemic vascular resistance, and these patients were analyzed together; the data of the only nonresponder is presented separately.

Hormonal assay: Plasma renin activity, plasma aldosterone, norepinephrine and angiotensin II levels were determined by radioimmunoassay.[11–13] Plasma renin activity was estimated by the generation of angiotensin I in vitro. Angiotensin II was separated from angiotensin I by high-pressure liquid chromatography and measured by radioimmunoassay. Norepinephrine levels were determined by radioenzymatic assay.

Statistical analysis: Values for the group are represented as mean ± standard error of the mean. Statistical determinations were by analysis of variance, with peak response compared to baseline values. Changes were considered to be statistically significant at the $p < 0.05$ level.

Results

The neurohormonal and hemodynamic effects of intravenous enalapril are shown in Figure 1. The baseline renin-angiotensin system activity was increased, with a mean plasma renin activity of 16.8 ± 6 ng/ml/hour, plasma aldosterone of 46 ± 14 ng% and angiotensin II of 68 ± 12 pg/ml. After the first bolus injection, there was an immediate and marked increase in plasma renin activity, with a more than 300% increase as early as 15 minutes. Peak response occurred at 30 minutes, increasing from a baseline value of 16.8 ± 6 ng/ml/hour to 86.6 ± 23 ng/ml/hour ($p < 0.05$). This effect was maintained with minor attenuation so that plasma renin activity was 72.4 ± 16 ng/ml/hour at the end of the 90-minute observation period. There was a progressive, time-delayed decrease in circulating plasma aldosterone levels, from a baseline of 46 ± 14 ng% to a nadir of 25 ± 6 ng% at 90 minutes after the first dose ($p < 0.05$). Norepinephrine levels were increased at baseline (561 ± 95 pg/ml), consistent with severe CHF, and did not show any significant change despite abrupt converting-enzyme inhibition.

The hemodynamic changes after intravenous enalapril therapy were also abrupt and peak changes occurred

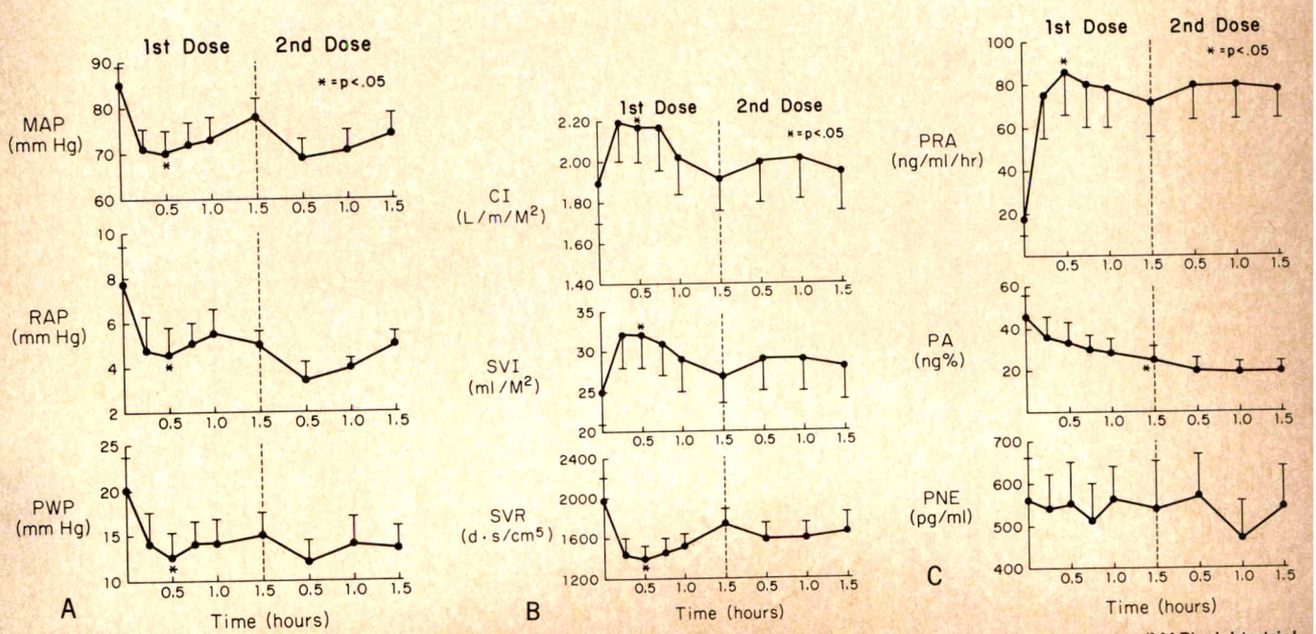

FIGURE 1. Hemodynamic and neurohormonal responses to bolus injections of intravenous enalapril. **A,** mean arterial pressure (MAP), right atrial pressure (RAP) and pulmonary capillary wedge pressure (PWP). **B,** cardiac index (CI), stroke volume index (SVI) and systemic vascular resistance (SVR). **C,** plasma renin activity (PRA), plasma aldosterone (PA) and plasma norepinephrine (PNE). Values are mean ± standard error of the mean.

TABLE I Hemodynamic and Neurohormonal Response to Intravenous Enalapril in a Nonresponder

	Baseline	15 min	30 min	60 min	90 min
MAP (mm Hg)	88	89	87	82	78
PWP (mm Hg)	25	21	18	19	24
CI (liters/m/m^2)	1.49	1.49	1.60	1.56	1.51
SVR (dynes s cm^{-5})	2,304	2,397	2,289	2,141	2,039
PRA (ng/ml/hour)	1.1	1.1	1.1	1.1	1.3
PA (ng%)	19	12	10	8.7	11
AII (pg/ml)	14.9	14.4	14.4	10.9	31.8
PNE (pg/ml)	842	753	654	807	932

AII = angiotensin II; other abbreviations as in Figure 1.

at 30 minutes. There was a prompt and marked reduction of systemic vascular resistance, from 1,974 ± 223 to 1,400 ± 136 dynes s cm^{-5}, and mean arterial pressure, from 85 ± 4 to 70 ± 5 mm Hg, at peak response ($p < 0.05$). Likewise, the decrease of right atrial pressure from 8 ± 2 to 5 ± 1 mm Hg and pulmonary wedge pressure from 21 ± 4 to 13 ± 3 mm Hg were both significant at peak response at 30 minutes ($p < 0.05$). Vasodilatation induced by abrupt converting-enzyme inhibition resulted in improved forward flow: Cardiac index increased from 1.88 ± 0.19 to 2.20 ± 0.21 liters/m/m^2 and stroke volume index from 25 ± 4 to 32 ± 4 ml/m^2 at peak response ($p < 0.05$). At the end of the 90-minute observation period, these hemodynamic changes were attenuated.

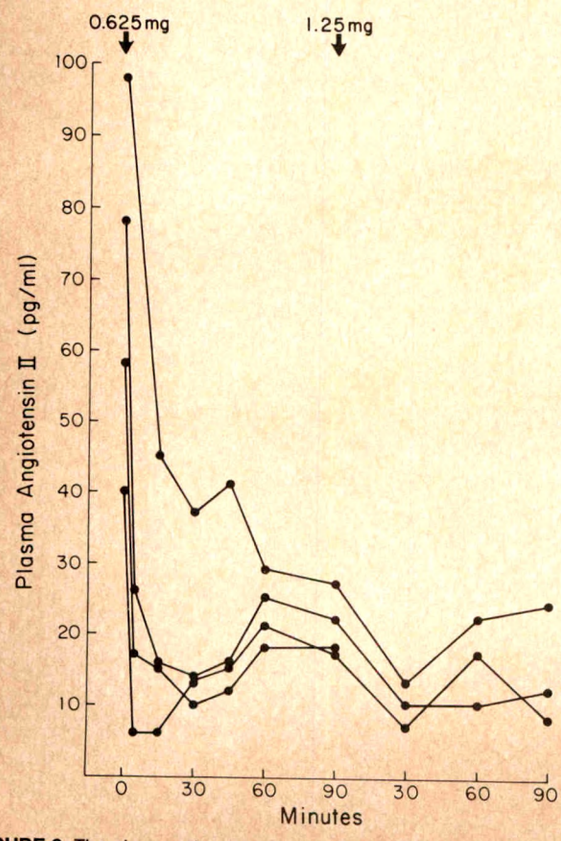

FIGURE 2. The changes in plasma angiotensin II levels after bolus injections of intravenous enalapril in 4 patients.

A second intravenous bolus of enalapril was then given to determine whether a cumulative response would occur and also to document complete converting-enzyme inhibition. After the second dose, the additional changes of plasma renin activity and plasma aldosterone levels were insignificant. All hemodynamic indexes show a trend of response similar to the first dose response, but there were no significant cumulative effects.

The lack of a cumulative response to the second dose of enalapril could represent either acute tachyphylaxis or maximal converting-enzyme inhibition maintained from the first dose. To clarify this issue, we examined the response of angiotensin II levels in 4 patients. Despite a wide range of baseline angiotensin II levels (40 to 98 pg/ml, mean 68 ± 12), angiotensin II decreased to 19 ± 6 pg/ml at 30 minutes. This effect was maintained over 90 minutes with minimal attenuation; after the second dose of enalapril, angiotensin II remained at comparable low levels.

The hemodynamic and neurohormonal changes of the only patient who did not respond to enalapril are listed in Table I. In this patient, the renin-angiotensin system was not activated, as manifest by baseline values for plasma renin activity of 1.1 ng/ml/hour, plasma aldosterone of 19 ng% and angiotensin II of 14.9 pg/ml, all of which are low relative to the other patients and essentially normal. Despite the differences in these baseline neurohormonal measurements, baseline hemodynamic indexes are similar to those of the other patients, suggesting the predominance of an alternate vasoconstrictor mechanism. Administration of intravenous enalapril had virtually no effect, confirming the minor contribution of angiotensin II–mediated vasoconstriction in this patient.

Discussion

The results of the present study demonstrate that the renin-angiotensin system can be abruptly and completely blocked by intravenous bolus injections of an active converting-enzyme inhibitor, enalapril (MK-422). The neurohormonal effects of converting-enzyme inhibition are manifest as early as 15 minutes, with peak effect at 30 minutes. This consists of an abrupt reduction in levels of circulating angiotensin II and an increase in plasma renin activity as a result of the reduction in angiotensin II negative feedback inhibition on renin secretion. In contrast to these abrupt changes,

there was a progressive, time-delayed decrease in the aldosterone level; this has been seen after oral administration of captopril and is related to the longer half-life of circulating aldosterone.[6]

Peak hemodynamic effect also occurred at 30 minutes. The reductions of systemic vascular resistance and mean arterial pressure were generally well tolerated and demonstrated some attenuation by 90 minutes. The magnitude of increases of cardiac index and stroke volume index at peak effect were significant, but were less than those seen with direct vasodilators, such as nitroprusside and the newer inotropic agents.[14] The improvements in forward flow seen with balanced vasodilators represent the net effect of reductions of afterload and reductions of preload. The specific influence of preload reduction with converting-enzyme inhibitors on the subsequent improvement in forward flow, however, has not been clarified.

Despite the rapid vasodilatation and decreases in mean arterial pressure, there was no reflex increase in heart rate. The lack of reflex sympathetic stimulation is confirmed by the lack of significant changes in plasma norepinephrine levels. Several investigators have described profound bradycardia after administration of captopril to some patients with CHF.[15] In the present study, no patient had bradycardia; although the study population was small, this finding suggests that bradycardia will not be a significant problem accompanying angiotensin II withdrawal with intravenous enalapril.

An inverse correlation between serum sodium concentration and plasma renin activity has been reported.[16,17] Our experience with a larger group of 108 patients with CHF confirms this relation.[18] However, this correlation is complex, as many patients with normal sodium levels have high renin levels, and is strongly influenced by diuretic therapy.[17] In the present small study, there was no correlation between sodium concentration and plasma renin activity.

The response of norepinephrine to vasodilator therapy is complex. Although a reduction in norepinephrine levels with long-term captopril therapy have been shown,[19] the response with long-term enalapril therapy has been inconsistent.[9,20] In the present study with intravenous enalapril, norepinephrine levels did not change acutely.

The insignificant hemodynamic and neurohormonal changes after the second bolus injection suggest that there are no cumulative effects of intravenous enalapril. A dose-response relation may be produced if even smaller doses of intravenous enalapril are used. However, the doses used in the present study (0.625 and 1.25 mg) are already low and smaller than the doses (5 to 10 mg) reported to be necessary in patients with hypertension.[21] At these larger doses, it is possible that an alternate mechanism, such as inhibition of bradykinin degradation, is activated. Our data suggest that such large doses may be excessive for patients with CHF and may be associated with adverse side effects.

The reduction in angiotensin II levels after intravenous enalapril treatment directly quantitate the inhibition of converting enzyme. The fact that they remain suppressed for 90 minutes after the first dose and do not show any appreciable change after the second dose strongly suggests complete inhibition of converting enzyme rather than acute tachyphylaxis. This is also helpful in explaining the lack of cumulative hemodynamic and neurohormonal effects from the additive doses. Unlike nonspecific vasodilators such as hydralazine, with which successive doses produce incremental responses, the effectiveness of converting-enzyme inhibitors is based on specific enzymatic inhibition, where dose responsiveness is unlikely.

Although only 1 patient in this small study did not respond to enalapril, this finding emphasizes 3 important features of the renin-angiotensin system and vasoconstrictor mechanisms in chronic CHF: (1) Baseline levels of plasma renin activity, plasma aldosterone and angiotensin II were low, emphasizing that the activation of the renin-angiotensin system in CHF varies from patient to patient.[4] (2) Despite the absence of renin-angiotensin system activation in this patient, hemodynamic severity of CHF and vasoconstriction were similar to those of the other patients in this study, thus supporting the concept of alternate vasoconstrictor mechanisms in CHF.[1] (3) Intravenous enalapril produced no significant hemodynamic or neurohormonal changes, confirming the minor contributions of angiotensin II–mediated vasoconstriction for this patient.

The use of pharmacologic probes, such as rapidly acting converting-enzyme inhibitors, may more accurately profile pathophysiologic mechanisms of vasoconstriction in CHF, so that vasodilator therapy can be specific and directed. As in earlier studies with converting-enzyme inhibitors in patients with CHF,[15] some patients will have marked reductions in blood pressure, so that careful monitoring of the acute hemodynamic effects is important. The present study has shown that intravenous enalapril is a useful pharmacologic probe of the renin-angiotensin system in chronic CHF. With abrupt and complete inhibition of converting enzyme, the contribution of angiotensin II–mediated vasoconstriction to the abnormal hemodynamic state can be assessed accurately.

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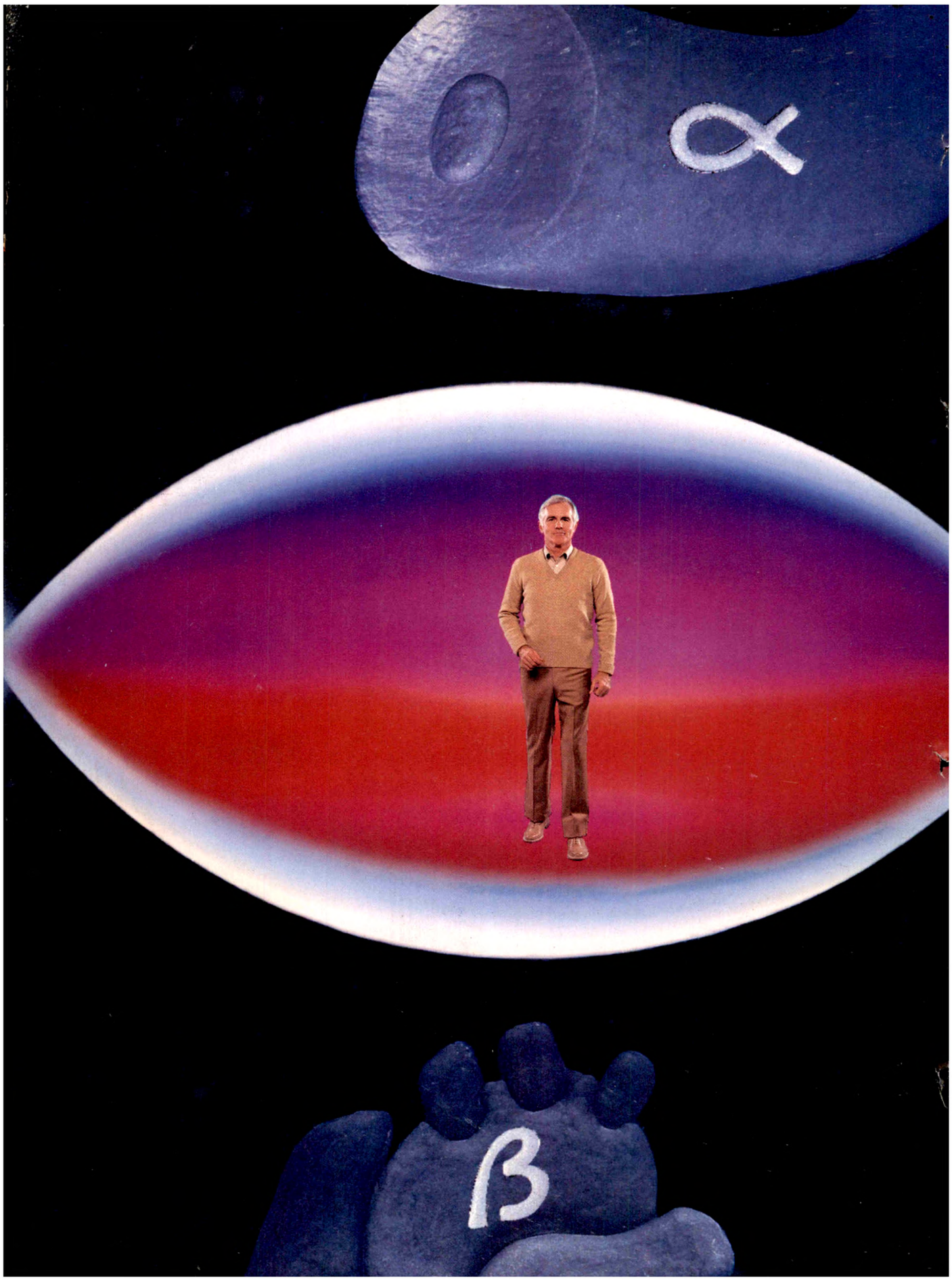
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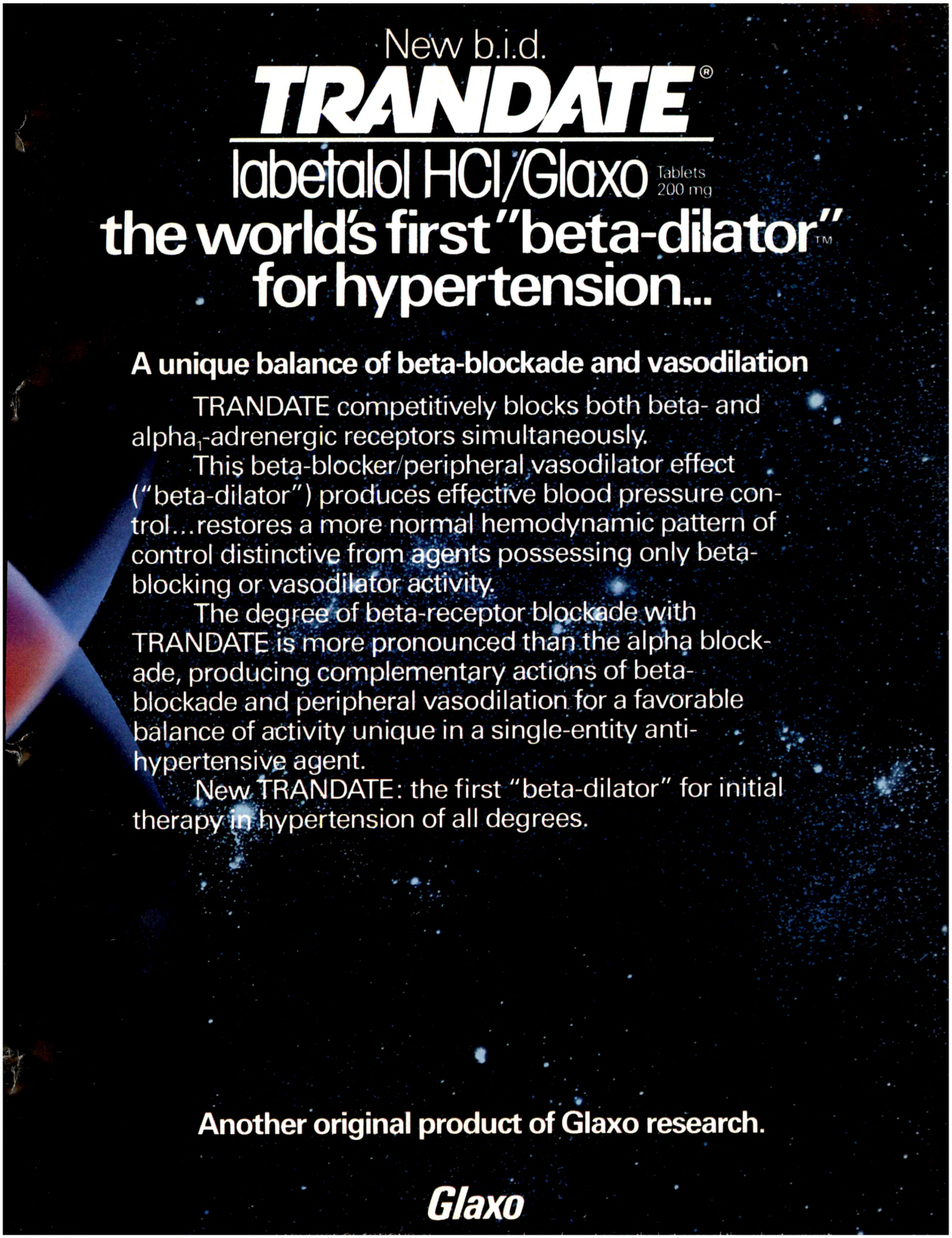
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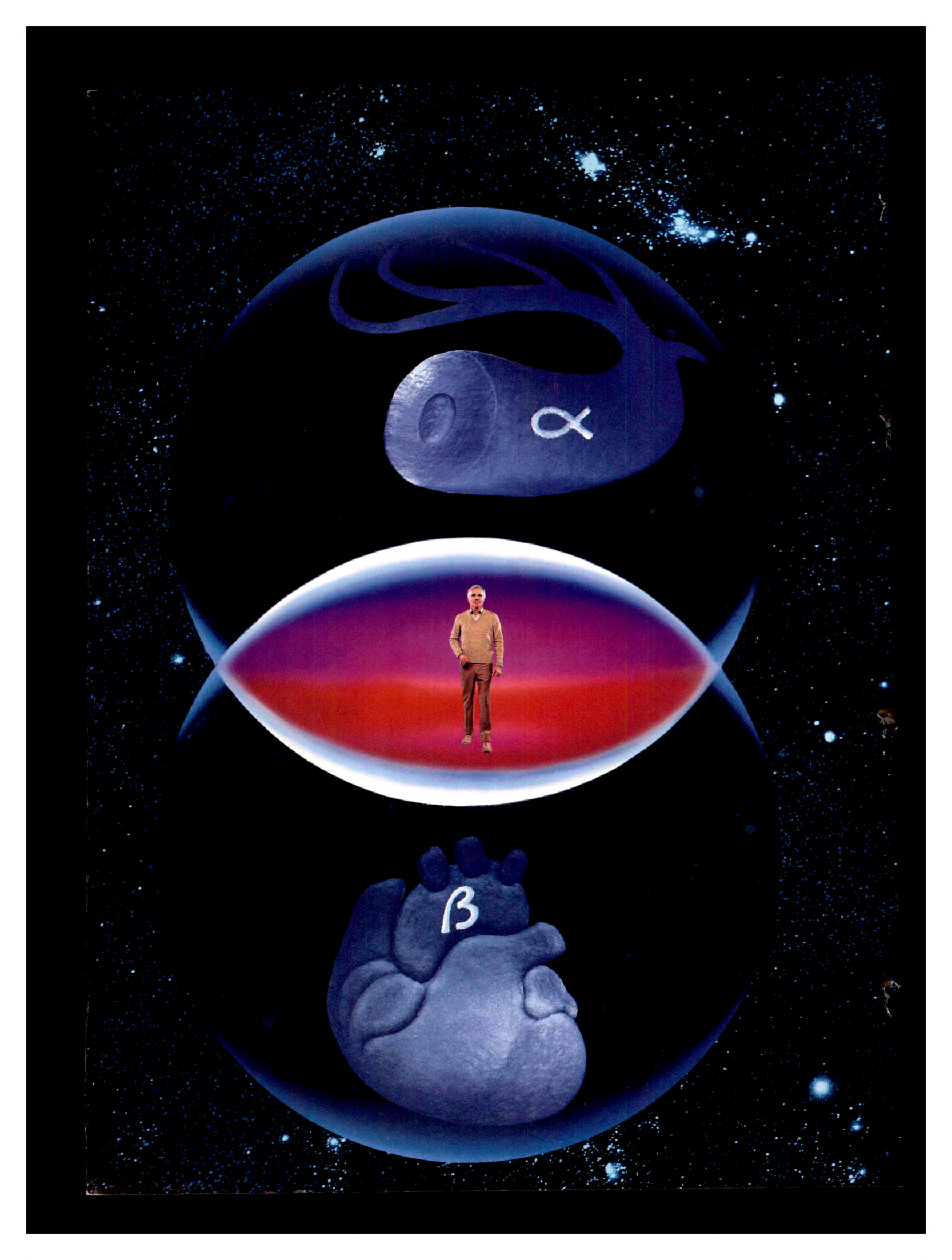
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Vasodilator-induced reflex tachycardia has not been re with TRANDATE therapy, nor has significant reduction in h rate. And beta-blocker-induced vasoconstriction does not o with TRANDATE, offering protection against cold extremities

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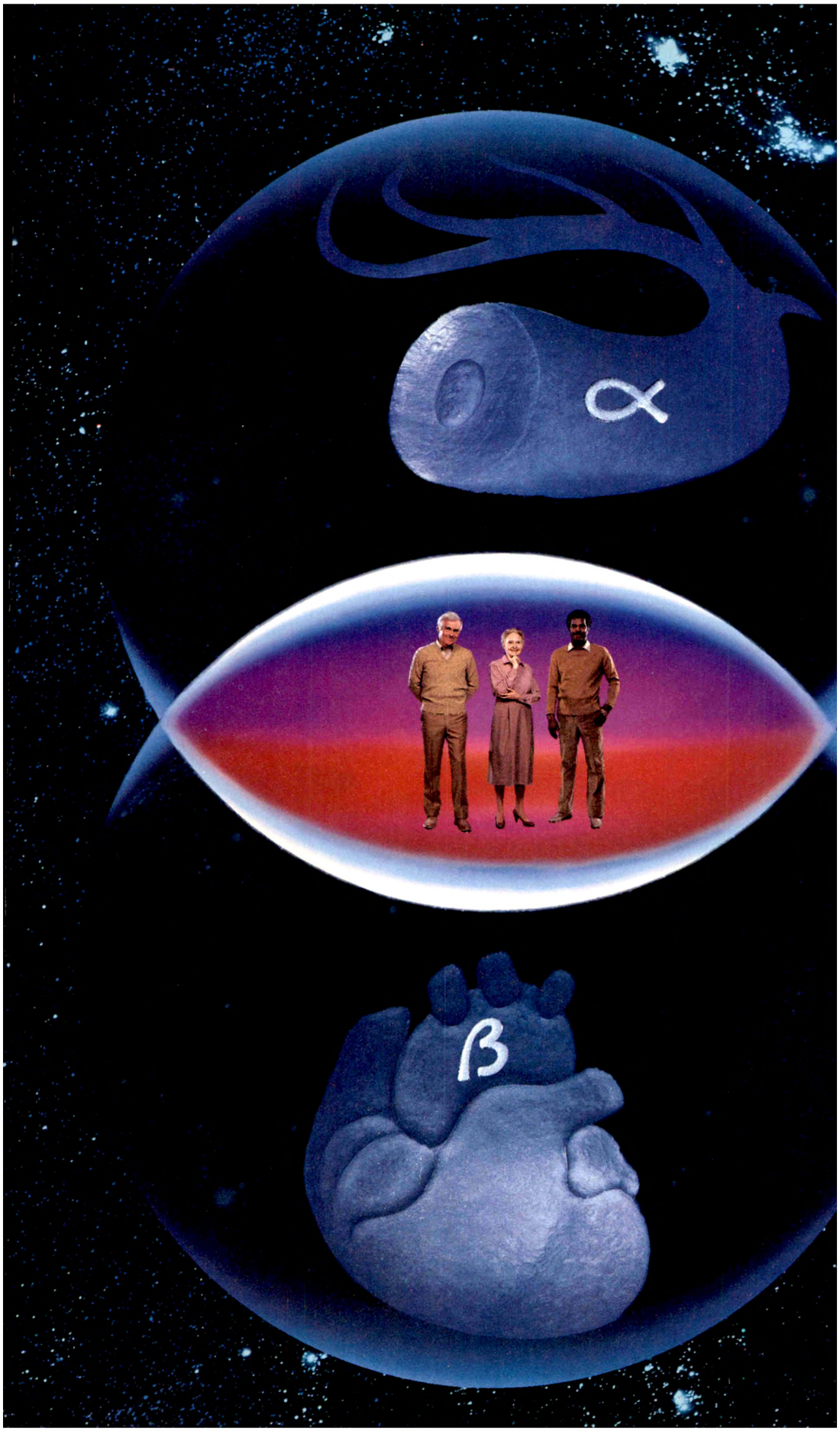
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Initiation of therapy with TRANDATE is simple. Low doses are used; initiate therapy with 100 mg (1/2 tab) b.i.d. and titrate upward as needed.

Most adverse effects are mild, occur early in treatment, and disappear during the first two weeks*

The most frequently reported reactions to TRANDATE in clinical trials were dizziness (11%) and nausea (6%); less frequent reactions (5% or less): fatigue, dyspepsia, nasal stuffiness, headache, edema, dyspnea, vertigo, rash, and postural hypotension.*

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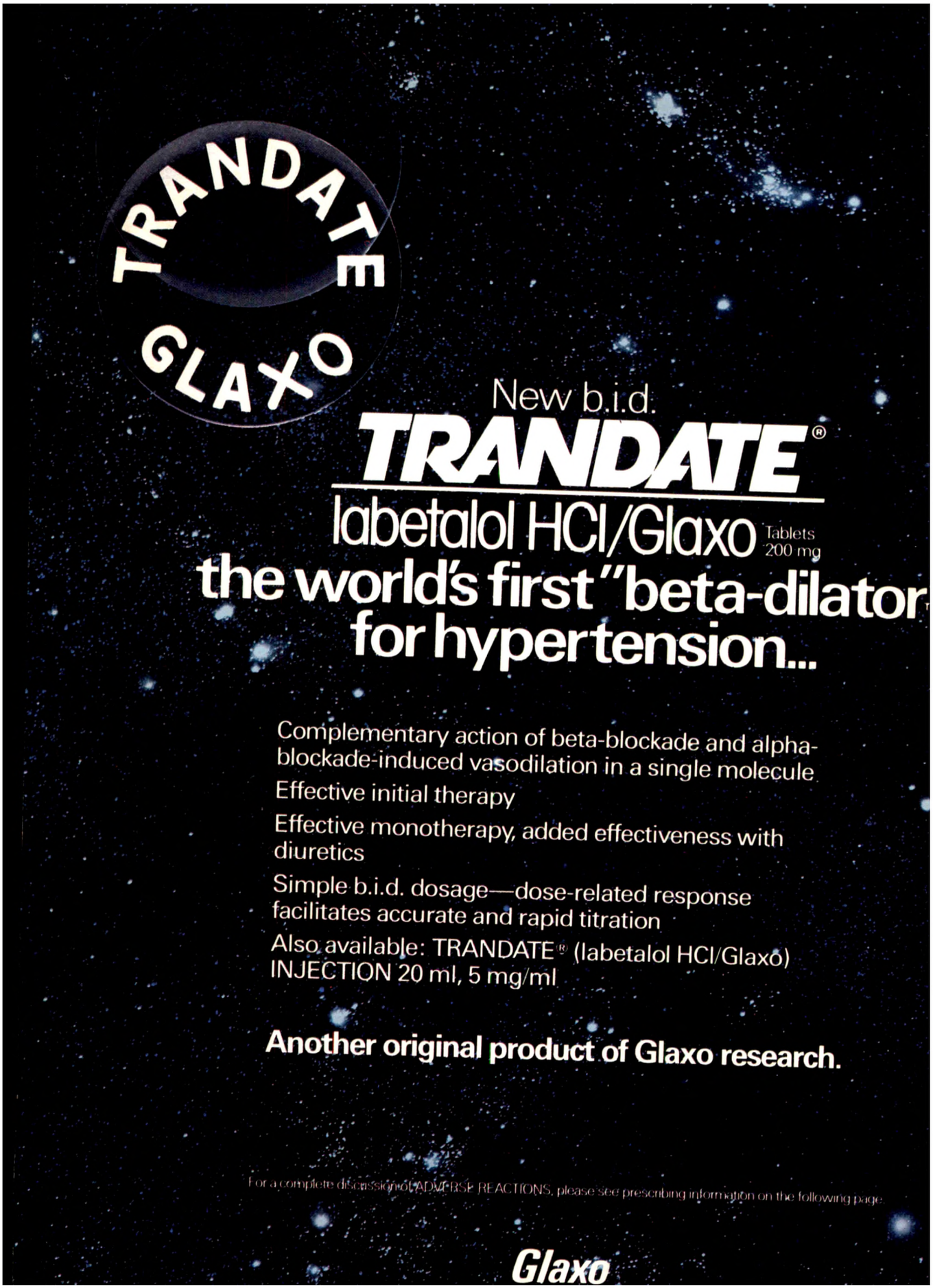
*Please see the last page of this advertisement for prescribing information, which includes a complete listing of incidence of reported ADVERSE REACTIONS at various dose levels.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·TRANDATE® Tablets
(labetalol hydrochloride)
BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: TRANDATE® (labetalol hydrochloride) Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, chronic bronchitis and emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Betablockade also reduces the release of insulin in response to hypoglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see Drug Interactions under PRECAUTIONS).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C: Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gesta- [illegible] doses of 3 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE® (labetalol HCl) Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy:

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose in the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose-related.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps; toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Overdosage with TRANDATE® (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: **Excessive bradycardia**—administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac failure**—administer a digitalis glycoside and a diuretic. **Hypotension**—administer vasopressors, eg, norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. **Bronchospasm**—administer a $beta_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dose is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg b.i.d. every 2 or 3 days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first 1 to 3 hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered b.i.d., the same total daily dose administered t.i.d. may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg b.i.d.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of TRANDATE® Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, TRANDATE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED: TRANDATE® Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43), bottles of 500 (NDC 0173-0347-44), and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43), bottles of 500 (NDC 0173-0348-44), and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F).

TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

Issued: August 198[illegible]

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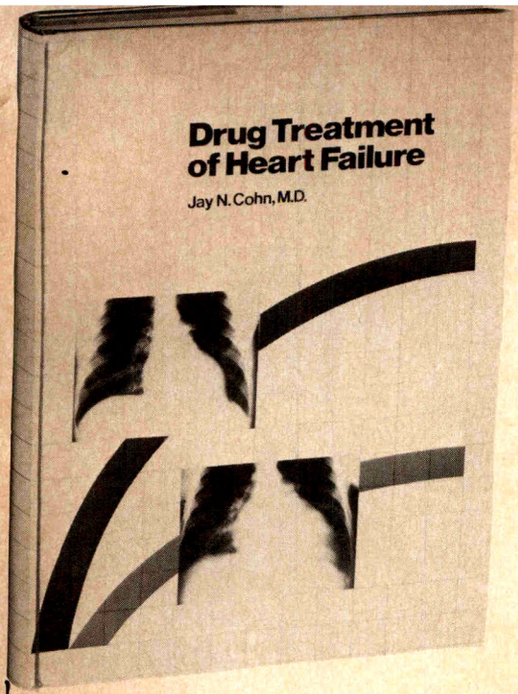
Glaxo Inc., Research Triangle Park, NC 27709



Drug Treatment of Heart Failure

edited by Jay N. Cohn, MD

0-914316-41-9, approx. 250pp., Oct. '83, $35.00

This volume is aimed at providing clinicians with the physiologic and pharmacologic background necessary to effectively and efficiently create and administer drug therapy regimens for their patients who suffer heart failure. All efforts were made to ensure that the timeliness of each chapter, prepared by internationally respected clinicians and medical scientists, would not be compromised by delays in publication. Consequently, this book presents the very latest thinking on the utilization of drug therapy for heart failure and contains many references as recent as 1982 and 1983. This book is highly recommended to all physicians presently treating patients with heart failure.

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Pattern of Left Ventricular Diastolic Filling in Chronic Aortic Regurgitation: A Gated Blood Pool Assessment

STEVEN J. LAVINE, MD, WILLIAM P. FOLLANSBEE, MD, DAVID P. SHREINER, MD, VENKATARAMAN KRISHNASWAMI, MD, P. S. REDDY, MD, and KAREN S. McKEE

Limited information exists regarding the pattern of left ventricular diastolic filling in moderate to severe chronic aortic regurgitation (AR). The left ventricular diastolic filling curve derived from gated blood pool scans was evaluated in 24 normal subjects and 29 patients with AR. The peak filling rate (PFR), mean filling rate (MFR), peak ejection rate (PER), PFR/MFR, PFR/PER, and the time of the rapid filling period divided by the diastolic time were determined. PFR, MFR and PER were calculated as end-diastolic volumes per second (EDV/s). PFR was lower in the AR group than in the normal subjects (2.24 ± 0.70 vs 3.09 ± 0.71 EDV/s, p <0.001). Similarly, MFR was lower in the AR group (1.31 ± 0.40 vs 1.63 ± 0.29 EDV/s, p <0.01). PER was also reduced in the AR group. Both PFR/MFR and PFR/PER were reduced, while the ratio of rapid filling period to diastolic time was longer in the AR group than in normal subjects. Clinical evidence of congestive heart failure occurred in 8 patients in the AR group. Diastolic filling variables were not significantly different from the asymptomatic subgroup of patients with AR, but were abnormal when compared with those of normal subjects. In patients with AR, an abnormal pattern of diastolic filling was noted, consisting of a reduced PFR, MFR and PFR/PER with a more linear pattern of filling (reduced PFR/MFR) during a longer rapid filling period.

(Am J Cardiol 1985;55:127–132)

Left ventricular (LV) diastolic filling has been described in patients with coronary artery disease,[1–6] systemic hypertension,[7,8] constrictive pericarditis,[9] restrictive[9] and hypertrophic cardiomyopathy[11–13] and valvular heart disease.[5,10,11,14] Specific patterns of diastolic filling have been described for coronary artery disease,[4,8] hypertension,[8] and for mitral and aortic regurgitation.[14] Although diastolic filling of the left ventricle has been extensively described in coronary artery disease, only limited information is available about diastolic filling in chronic aortic regurgitation (AR). The limited data available are conflicting. One study suggested that normal patterns of LV diastolic filling are present in asymptomatic patients, whereas an abnormal and delayed pattern of filling is present in patients with symptoms that suggest congestive heart failure.[14] A second study has noted a reduced peak filling rate (PFR) and a reduced percent stroke volume filled at the time of the PFR in a group of patients with chronic AR awaiting valve replacement.[10] This study evaluates the pattern of diastolic filling in patients with moderate to severe chronic AR using gated blood scintigraphy.

From the Section of Cardiology and Nuclear Medicine, Veterans Administration Medical Center and Presbyterian-University Hospital, University of Pittsburgh, Pittsburgh, Pennsylvania. Manuscript received July 2, 1984; revised manuscript received August 14, 1984, accepted August 20, 1984.

Address for reprints: Steven J. Lavine, MD, Section of Cardiology, Veterans Administration Medical Center, University Drive C, Pittsburgh, Pennsylvania 15240.

Methods

Patients: We performed gated blood pool scintigrams in 24 patients referred for cardiac catheterization for evaluation of chest pain who had normal coronary arteries with normal LV function (group 1) and in 29 patients with angiographically demonstrated moderate to severe chronic AR (group 2). Of the 29 patients with AR, 21 were asymptomatic and 8 had symptoms of congestive heart failure (dyspnea on exertion, fatigue, orthopnea, and so on). Of the asymptomatic patients, 16 were referred for increasing heart size and 5 for cardiomegaly. Twelve-lead electrocardiograms were performed in all patients. Eighteen of 24 normal patients (75%) and all patients with chronic AR had M-mode and 2-dimensional echocardiograms. All patients with other valvular heart disease, cardiomyopathy, coronary artery disease or coronary artery spasm were excluded.

All group 1 patients with LV hypertrophy were excluded. The presence of LV hypertrophy was assessed by voltage and other electrocardiographic criteria of Romhilt and Estes[15] or by the septal or posterior wall thickness of 12 mm or more on

TABLE I Age, Intervals, Ejection Fraction, Volumes and End-Diastolic Pressure

	Normal (n = 24)	AR (n = 29)
Age (yr)	53 ± 10	51 ± 15
RR (ms)	862 ± 130	871 ± 137
DT (ms)	544 ± 94	555 ± 116
EF (%)	66 ± 7	61 ± 11*
EDV (ml)	154 ± 31	231 ± 46†
SV (ml)	102 ± 16	141 ± 23†
EDP (mm Hg)	8 ± 3	14 ± 7†

* $p < 0.05$; † $p < 0.001$ vs values in normal subjects.
AR = aortic regurgitation; DT = diastolic time; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; RR = RR interval; SV = stroke volume.

the M-mode echocardiogram. Normal LV function in group 1 was defined as an ejection fraction greater than 50%, no electrocardiographic evidence of prior myocardial infarction (Q waves longer than 40 ms), the absence of regional wall disease as determined by both contrast ventriculography and gated blood pool scintigraphy, a normal end-diastolic pressure (less than 13 mm Hg), and a normal end-diastolic volume index (<95 ml/m^2). Exercise testing in 18 group 1 patients revealed nondiagnostic electrocardiographic responses in 14, negative responses in 4, and atypical chest pain being induced in 4 patients. Beta- and calcium channel-blocking drugs were discontinued for 72 hours, whereas long-acting nitrates were discontinued 8 hours before cardiac catheterization and gated blood pool scintigraphy in both groups.

Cardiac catheterization: Coronary arteriography, left- and right-sided cardiac catheterization, and contrast left ventriculography, were performed in both groups of patients. Aortic root injection was performed in all patients with chronic AR. AR was graded on a scale of 1 to 4 by 2 independent observers. Agreement occurred in 23 patients. Only 1 observer determined the degree of AR in the other 6 patients. Only patients with grade 3 or 4 (moderate to severe) AR were included in the analysis. Regional wall motion was interpreted as qualitatively normal or abnormal by 2 independent observers. Agreement occurred in all group 1 patients. In group 2 patients, agreement occurred in 26 of 29 patients. Only observer determined regional wall motion in the other 3 patients. In group 2, global hypokinesia was noted in 5 patients and regional wall disease in none.

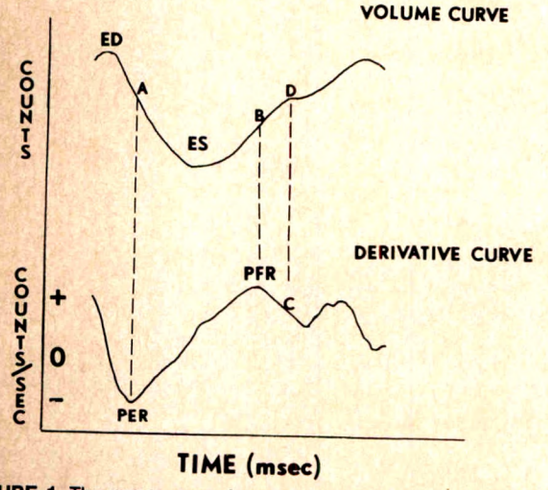

FIGURE 1. The **upper curve** is a representation of a left ventricular volume curve derived from gated blood pool scintigraphy. The **lower curve** is the first derivative of the left ventricular volume curve. Point A is the volume at which the peak ejection rate (PER) occurs. Point B is the volume at which the peak filling rate (PFR) occurs. Point C represents the point on the derivative curve following PFR, which is 20% of PFR. This point is time represents the end of the rapid filling period. The corresponding point in time (D) on the volume curve represents the volume at the end of the rapid filling period. ED = end-diastole; ES = end-systole.

Gated blood pool cardiac scintigraphy: Gated blood pool scintigraphy was performed in the supine position within 4 hours of cardiac catheterization. Before imaging, red blood cells were labeled in vivo with 20 to 25 mCi of technetium-99m. Imaging was performed with a conventional gamma camera and a medium-sensitivity, all-purpose, parallel-hole collimator in the anterior view, in the modified left anterior oblique view that best separated the left from the right ventricle, and in the left lateral view. Image collection was synchronized with the QRS complex of the electrocardiogram by a computer-based electrocardiographic gate (American Optical). A commercial computer system (MDS-A2) divided each cardiac cycle into 32 frames. Images were acquired in a 64 × 64-byte mode matrix for at least 250,000 counts/frame. A plot of the number of cycles collected for each RR interval was inspected. If 99% of the cycles fell within 10% of this average RR interval, then the study was further analyzed (similar to serial mode acquisition with a 10% window). If not, it was excluded because of the likelihood that the rapid filling period may not be accurately represented.[3] Five patients in group 1 and 4 patients in group 2 were excluded.

LV regions of interest were derived for each frame by a semiautomatic second derivative edge-detection algorithm (MUGE) applied to each of the frames. A paraventricular background region of interest was selected by the algorithm. A background subtracted time-activity curve was generated using temporal averaging and spatial smoothing of the image sequence. The resulting curve was subjected to a 5-point smoothing routine. The ejection fraction was calculated from the background subtracted time-activity curve in the standard manner. Regional wall motion was qualitatively assessed as *normal or abnormal* by 2 independent observers for each of the 3 views. Interobserver agreement occurred in 100% of group 1 patients and in 27 of 29 patients in group 2. In group 2, 2 patients produced discordant readings, which were resolved by a single observer. In group 2 patients, global hypokinesia was noted in 5 patients and regional disease in none.

End-diastolic and end-systolic volumes were determined in each patient from the gated blood pool scintigram by a variation of a previously described, count-based, nongeometric method,[16–18] which was validated in our laboratory in 31 other patients. A close correlation was noted between end-diastolic radionuclide volume units and end-diastolic volume by contrast ventriculography (angiographic volume = 4.14 [radionuclide volume units] + 60.1 ml: $r = 0.96$, $p < 0.001$). There was also a close correlation between end-systolic radionuclide volume units and end-systolic volume by contrast ventriculography (angiographic volume = 4.4 [radionuclide volume units] + 19.8 ml: $r = 0.97$, $p < 0.001$). The standard error of estimate was ±19.1 ml for end-diastole and ±16.2 ml for end-systole. End-diastolic and end-systolic radionuclide volume units were calculated for each patient and converted to end-diastolic and end-systolic volume by use of the regression equations noted before. Stroke volume was determined by subtracting end-systolic volume from end-diastolic volume. For the 24 normal subjects and 29 patients with AR, excellent correlations were found with contrast ventriculography for end-diastole ($r = 0.95$) and end-systole ($r = 0.96$).

ABLE II Systolic Ejection and Diastolic Filling Rates

	Normal Subjects (n = 24)	Patients with AR (n = 29)
PER (EDV/s)	4.01 ± 0.88	3.39 ± 0.91*
PFR (EDV/s)	3.09 ± 0.71	2.24 ± 0.70†
MFR (EDV/s)	1.63 ± 0.29	1.31 ± 0.40‡
PFR/MFR	1.89 ± 0.23	1.70 ± 0.35*
PFR/PER	0.79 ± 0.21	0.67 ± 0.16*

* $p < 0.05$; † $p < 0.001$ vs values in normal subjects; ‡ $p < 0.01$.
AR = aortic regurgitation; EDV/s = end-diastolic volumes per second; MFR = mean filling rate; PER = peak ejection rate; PFR = peak filling rate.

TABLE III Diastolic Time Intervals and Percent Filling at These Intervals

	Normal Subjects (n = 24)	Patients with AR (n = 29)
TPER (ms)	107 ± 47	105 ± 34
TPFR/DT	0.33 ± 0.07	0.36 ± 0.16
RFP (ms)	294 ± 52	354 ± 84*
RFP/DT	0.54 ± 0.11	0.64 ± 0.11*
% SV-1/3 DT (%)	46 ± 14	44 ± 13
% SV-PFR (%)	40 ± 11	39 ± 14
% SV-RFP (%)	72 ± 13	75 ± 13

* $p < 0.01$ vs values in normal subjects.
AR = aortic regurgitation; RFP = rapid filling period; RFP/DT = rapid filling period/diastolic time; % SV-1/3 DT (%) = percent stroke volume filled at one-third of diastole; (divided by the RR interval); % SV-PFR = percent stroke volume filled at the time of the peak filling rate; % SV-RFP = percent stroke volume filled at the end of the rapid filling period; TPER = time to peak ejection rate; TPFR/DT = time to peak filling rate/diastolic time.

The time-activity curve is analogous to a plot of volume against time. In Figure 1, end-diastole is the highest part of the upper curve, while end-systole represents the nadir of the curve. The time elapsed from end-systole to the next end-diastole is the diastolic time. The lower curve in Figure 1 is the first derivative of the time-activity curve and is a plot of counts per second vs time. The nadir of the derivative curve represents the peak ejection rate. Point A on the volume curve represents the volume at which the peak ejection rate (PER) occurs. The time elapsed from end-diastole to point A is the time to PER. The maximal value of the first positive deflection on the derivative curve is the PFR. Point B on the volume curve is the volume at which the PFR occurs. The time elapsed from end-systole to point B is the time to PFR and was divided by the diastole time to take into account the effect of heart rate. Point C on the derivative curve represents the time after PFR at which 20% of the PFR occurs and, as noted by Gibson and Brown,[10] represents the end of the rapid filling period. Point D on the volume curve represents the corresponding volume that marks the end of the rapid filling period. The time elapsed from end-systole to point D represents the rapid filling period, which was divided by the diastolic time to take into account the effect of heart rate. This period may not be a precise representation of the rapid filling period because it unavoidably contains the isovolumic relaxation period. The volume filled from end-systole to point D divided by the rapid filling period represents the mean filling rate (MFR) of the rapid filling period. If after PFR, the filling rate did not decrease to exactly 20% of PFR before atrial systole, then the point on the derivative curve that was closest to 20% of the PFR was chosen. The filling rate decreased to less than 30% of the PFR in 49 patients. In each of the 49 patients, diastasis was discernible and corresponded to the first or second point of the diastatic plateau. In the other 4 patients, diastasis (plateau after the rapid filling period) could be clearly identified from the volume curve with complete agreement of 2 independent observers. The first point of diastasis was chosen as the end of the rapid filling period.

The PFR and MFR were expressed as counts per second and divided by end-diastolic counts yielding the PFR or MFR expressed as end-diastolic volumes per second (EDV/s). The percent stroke volume filled at the time of the PFR, at the end of the rapid filling period and at one-third of diastole were measured. Linear interpolation was used to determine the percent stroke volume filled at one-third of diastole if the time of one-third of diastole fell between 2 points on the time-activity curve. This measure was divided by the RR interval due to its high correlation (r = 0.86) with the heart rate.

The ratio PFR/MFR and the ratio of PFR/PER were determined as 2 additional filling indexes. PFR/MFR is an estimate of the linearity of flow during the rapid filling period. A value of 1 indicates a linear flow rate throughout the rapid filling period. The PFR/PER ratio takes into account the known relation between PFR and PER.[5]

Interobserver and intraobserver variability for PFR and MFR were determined in a separate group of 30 subjects: 9 normal subjects, 10 patients with coronary artery disease and normal LV function, and 11 patients with coronary artery disease and abnormal LV function. Interobserver variability was determined by 2 observers independently evaluating and generating the time-activity curve from the left anterior oblique view. The absolute value for interobserver variability was 0.10 ± 0.11 EDV/s for PFR and 0.05 ± 0.05 EDV/s for MFR. Intraobserver variability was determined by 2 separate generations of the time-activity curve by a single observer several weeks apart. The absolute value for intraobserver variability was 0.05 ± 0.05 EDV/s for PFR and 0.02 ± 0.03 EDV/s for MFR.

Statistics: All data are expressed as mean ± standard deviation. Comparison among groups was performed by unpaired *t* tests. When normal subjects were compared to patients with AR with and without heart failure, 1-way analysis of variance was used. If the F statistic was significant at 0.05 level, then *t* tests were used to find where the difference existed. Linear regression was performed to assess the relation between 2 variables.

Results

Table I is a summary of the results of age, RR interval, diastolic time, ejection fraction, end-diastolic volume and pressure, and stroke volume for normal subjects and patients with chronic AR. No significant differences were noted with regard to age, RR interval and diastolic time. The ejection fraction was slightly lower and the end-diastolic volume, stroke volume and end-diastolic pressure were higher in the AR group.

Systolic ejection and diastolic filling rates (Table II): PER, PFR and MFR were reduced in patients with AR. The PFR/PER was also reduced in patients with AR, suggesting that diastolic filling rates were reduced out of proportion to the reduction in PER. The PFR/MFR, an estimate of linearity of flow during the rapid filling period, was reduced in this group.

Diastolic time intervals and percent filling at these intervals (Table III): Of the measurements listed in Table III, only the rapid filling period and the rapid filling period/diastolic time were longer in patients

TABLE IV Ejection Fraction, Volumes, Timing Intervals and Diastolic Filling Measurements

	AR − CHF (n = 21)	AR + CHF (n = 8)
RR (ms)	879 ± 134	810 ± 52
DT (ms)	567 ± 118	516 ± 55
EF (%)	64 ± 9	50 ± 13*
EDV (ml)	215 ± 44	272 ± 33†
SV (ml)	143 ± 22	136 ± 24
EDP (mm Hg)	12 ± 6	19 ± 5‡
PFR (EDV/s)	2.36 ± 0.71	1.86 ± 0.78
MFR (EDV/s)	1.35 ± 0.38	1.18 ± 0.50
PFR/MFR	1.72 ± 0.32	1.63 ± 0.38
PFR/PER	0.68 ± 0.15	0.62 ± 0.18
RFP/DT	0.63 ± 0.13	0.68 ± 0.07
%SV-1/3 DT (%)	43 ± 13	49 ± 13
%SV-PFR (%)	42 ± 13	31 ± 15
%SV-RFP (%)	75 ± 13	76 ± 14

* $p < 0.05$; † $p < 0.001$; ‡ $p < 0.01$; aortic insufficiency without versus aortic insufficiency with congestive heart failure.
CHF = congestive heart failure; other abbreviations as in Tables I to III.

with AR. The reduction in MFR noted earlier was primarily a result of the longer rapid filling period, because the percent stroke volume filled at the end of the rapid filling period was similar in both groups. MFR is equal to the percent stroke volume filled at the end of the rapid filling period divided by the time of the rapid filling period. Figure 2 shows a time-activity curve normalized to end-diastolic counts for a normal patient and a patient with AR. In the patient with AR, diastolic filling appears more linear during a longer rapid filling period, and a reduced PFR is present.

Aortic regurgitation with congestive heart failure vs no congestive heart failure: Table IV is a summary of the results of ejection fraction, ventricular volume, timing intervals and diastolic filling measurements in patients with AR with and without clinical evidence of congestive heart failure. The ejection fraction was lower and the end-diastolic volume and pressure were higher in the AR subgroup with clinical evidence of congestive heart failure. However, diastolic filling values were similar in both AR subgroups. The asymptomatic subgroup still had higher end-diastolic volumes, stroke volumes and end-diastolic pressures than the normal group. PFR, MFR, PFR/MFR and PFR/PER were reduced while the rapid filling period/diastolic time was longer in the asymptomatic AR subgroup than in normal subjects.

Relation between RR interval, ejection fraction and filling indexes: In normal subjects and patients with AR, the average RR interval was unrelated to any filling variable (Table V). In normal subjects, the ejection fraction was related to PFR and MFR as EDV/s and to PFR/PER. In patients with AR, the ejection fraction was only related to PFR and MFR as EDV/s.

Discussion

Using gated blood scintigraphy, we evaluated the pattern of diastolic filling in 24 patients with normal coronary angiograms and 29 patients with moderate to severe chronic AR, 8 of whom had symptoms of congestive heart failure. Patients with moderate to severe chronic AR, as a group, had a slightly lower ejection fraction, but a higher end-diastolic volume, stroke volume and end-diastolic pressure than normal subjects. Diastolic filling was abnormal in patients with AR and was characterized by reduced PFR and MFR, a longer rapid filling period, and more linear rate of filling during the rapid filling period (reduced PFR/MFR). This pattern of diastolic filling is demonstrated in Figure 2 in a patient with severe AR. In our study, PER in the AR group was reduced. Because PFR and PER as EDV/s may be closely related,[5] PFR/PER was used to normalize PFR for PER. The PFR/PER was still reduced in the AR group.

In our group of 29 patients with AR, 8 patients had symptoms suggestive of congestive heart failure. This subgroup had a larger end-diastolic volume, higher

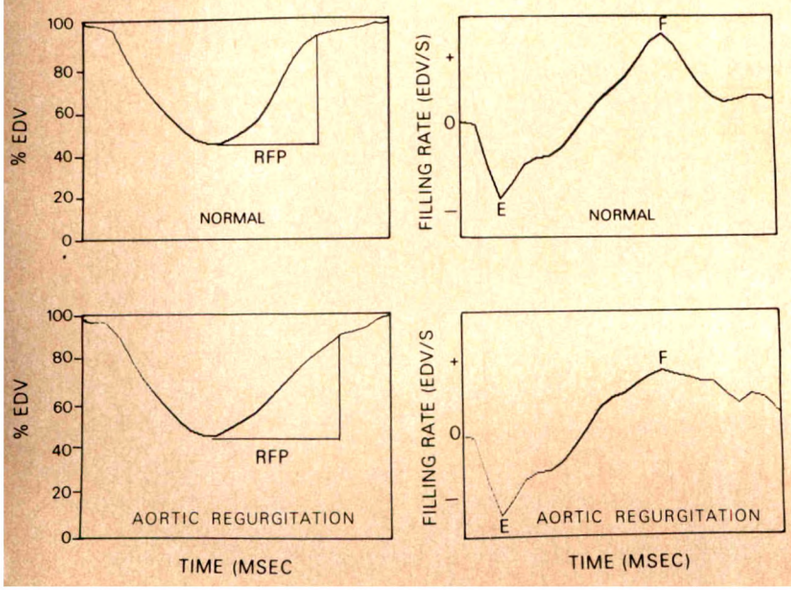

FIGURE 2. Time-activity curves for a normal patient (**top left**) and for a patient with aortic regurgitation (**bottom left**), expressed as percent end-diastolic volume (%EDV). The derivative curves expressed as end-diastolic volumes/second (EDV/s) are shown for both a normal patient (**top right**) and a patient with aortic regurgitation (**bottom right**). The diastolic filling curve is more linear in the patient with aortic regurgitation, with a longer rapid filling period (RFP) (**bottom left**) and a reduced peak filling rate (**bottom right**). E = peak ejection rate; F = peak filling rate.

end-diastolic pressure, and a lower ejection fraction than normal subjects or asymptomatic patients with AR (Table IV). When diastolic filling rates and intervals in the subgroup with coronary artery disease were compared with the asymptomatic subgroup, no significant differences were noted. Thus, the pattern of diastolic filling noted in the subgroup with congestive heart failure was similar, although accentuated, compared with the asymptomatic subgroup. The asymptomatic subgroup continued to demonstrate abnormal diastolic filling compared with normal patients despite the removal of the subgroup with congestive heart failure.

Our data appear to agree with the digitized M-mode findings of Gibson and Brown[10] in that PFR was reduced in patients with chronic AR. However, our data appear to be at variance with the biplane ventriculographic data of Osbakken and Bove.[14] This may be a result of the differing methods of analysis for diastolic filling. Osbakken and Bove[14] divided diastole into tenths and expressed diastolic filling as the percent of end-diastolic volume filled at each tenth of diastole. With regard to their asymptomatic patients, no differences were found at each tenth of diastole compared with normal subjects. However, diastolic filling was linear during diastole in both asymptomatic patients and those with congestive heart failure with AR. A point-by-point comparison throughout diastole should not be entirely relied on because it may not reveal the linearity of the filling curve. In addition, because the ejection fraction was lower in the subgroup with congestive heart failure, it can be anticipated that the percent of end-diastolic volume filled at each tenth of diastole in early diastole would be greater in subgroup with the lower ejection fraction (0% of diastole is equal to 1 minus the ejection fraction). This method of expressing filling is clearly ejection fraction–dependent.

Osbakken and Bove[14] also noted that the MFR of diastole, expressed as EDV/s, was greater in the asymptomatic subgroup of patients with AR. However, we noted a reduced MFR rate of the rapid filling period due to a longer rapid filling period in our comparable subgroup. The MFR of diastole in Osbakken's study was simply the ejection fraction divided by the diastolic filling time. In Osbakken's subgroup, the ejection fraction was slightly, but not significantly, higher and the diastolic filling time was not stated (but expected to be reduced). The elevated MFR of diastole may be a consequence of a higher ejection fraction and a shorter diastolic time. It is too general an index and does not adequately reflect events during the rapid filling period.

Several explanations are possible for the abnormal pattern of diastolic filling in patients with chronic AR. They include abnormal incremental elastance,[19] simultaneous filling from the anterograde mitral flow and retrograde aortic flow and abnormal stiffness.[20–22] Rousseau et al[19] demonstrated abnormal incremental elastance and a reduced velocity of lengthening in patients with chronic AR. Incremental elastance was defined as the change in pressure divided by the change in volume beginning at a common wall stress of 40 kdyne/cm^2 and ending when a 20-ml/m^2 volume increase in the left ventricle occurs. This measurement was made at a time when LV pressure was decreasing and LV volume was increasing. However, abnormal incremental elastance appeared to be confined only to patients with an elevated wall stress or reduced contractility. Because wall stress cannot be determined from radionuclide data, the role of incremental elastance cannot be assessed in our study.

TABLE V Correlation Coefficients Between RR Interval, Ejection Fraction and Filling Indexes

	Normal Subjects (24)		Patients with AR (29)	
	RR	EF	RR	EF
PFR (EDV/s)	−0.27	0.77*	−0.01	0.63*
MFR (EDV/s)	−0.12	0.79*	−0.27	0.65*
PFR/MFR	−0.32	−0.05	0.33	−0.03
PFR/PER	0.30	−0.57†	0.13	0.19

* $p < 0.001$ compared with $r = 0$; † $p < 0.01$.
Abbreviations as in Table II.

Another potential explanation for this pattern of diastolic filling may be simultaneous anterograde mitral flow and retrograde aortic flow. Continuous retrograde flow from the aortic root throughout diastole may distort the filling curve producing its linear appearance and lengthened rapid filling period. Because radionuclide techniques cannot quantitate the extent and timing of anterograde mitral flow and retrograde aortic flow separately, the role of diastolic regurgitant flow altering the filling pattern can not be assessed.

Several investigators[20–22] have noted that although the pressure-volume curve is shifted to the right, an abnormal LV chamber stiffness constant may be found in patients with chronic volume overload. However, chamber stiffness is measured at a time of small volume changes and may not reflect early diastolic filling. Furthermore, chamber stiffness constants were found not to correlate with PFRs.[23] Therefore, the role that abnormal LV chamber stiffness plays in patients with chronic AR is not clear.

Clinical implications and limitations of the study: An abnormal pattern of diastolic filling of the left ventricle has been noted in patients with moderate to severe chronic AR with and without symptoms of congestive heart failure. Our data do not allow differentiation of patients with congestive heart failure or more severe AR from those with less severe disease on the basis of the diastolic filling pattern. Further work is needed in describing diastolic filling in patients with varying extents of AR and in patients with heart failure due to chronic AR. Finally, a method of determining the amount, rate and time course of simultaneous aortic regurgitant flow and mitral anterograde flow may be useful in explaining the abnormal pattern of diastolic filling.

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Frequency of Mitral Valve Dysfunction from Mitral Anular Calcium as Detected by Doppler Echocardiography

ARTHUR J. LABOVITZ, MD, JEANNE G. NELSON, DENISE M. WINDHORST, HAROLD L. KENNEDY, MD, and GEORGE A. WILLIAMS, MD

Doppler echocardiography is useful for detecting and quantifying mitral regurgitation (MR) and mitral stenosis (MS). To determine the prevalence of these abnormalities in patients with mitral anular calcium (MAC), 51 consecutive patients who had an echocardiographic diagnosis of MAC were examined by Doppler ultrasound. Transmitral flow was evaluated to determine the presence of MR or left ventricular inflow obstruction (MS) by continuous and pulsed-wave Doppler echocardiography. The severity of these hemodynamic abnormalities was quantitated by previously described techniques. Eleven patients (22%) had mild MR, 17 (33%) had moderate to severe MR and 4 (8%) had significant MS. Clinical findings such as a systolic murmur, evidence of congestive heart failure, and dyspnea on exertion were not helpful in distinguishing patients with no or mild MR from those who had moderate to severe MR. M-mode measured left atrial size was significantly larger ($p < 0.05$) in patients with moderate to severe MR. This study suggests that MR is often associated with MAC, that MS is not a rare finding with MAC, and that Doppler echocardiography can quantitate these lesions in the elderly when symptoms are not specific and physical findings are inconclusive or absent.

(Am J Cardiol 1985;55:133–137)

Mitral anular calcium (MAC) is a frequent finding in elderly persons.[1–8] Autopsy studies performed in persons older than 50 years reveal that the prevalence is 10 to 15%, depending on age and gender.[9–13] Although radiologists have long recognized the characteristic C- or J-shaped opacity in the posterior-inferior portion of the cardiac silhouette on chest x-ray, only since the advent of echocardiography have clinicians recognized the frequency of this entity. Efforts to accurately assess the incidence of both mitral regurgitation (MR) and functional mitral stenosis (MS) in patients with MAC have been handicapped by the lack of invasive hemodynamic studies in large numbers of these patients, many of whom are elderly and not sufficiently symptomatic to warrant cardiac catheterization. Recent developments in Doppler technology have allowed us to evaluate noninvasively whether MAC has hemodynamic significance.[14–19] We evaluated the prevalence of MR and MS in a consecutive series of patients with MAC and correlated Doppler findings with standard echocardiographic and clinical characteristics.

From the Department of Internal Medicine, Division of Cardiology, St. Louis University School of Medicine, St. Louis, Missouri. Manuscript received July 5, 1984; revised manuscript received September 10, 1984, accepted September 11, 1984.

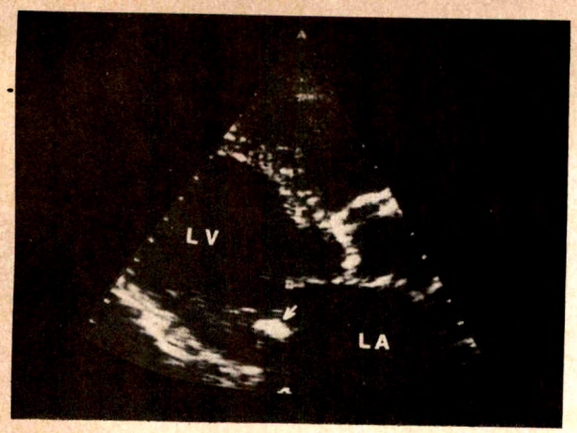
Address for reprints: Arthur J. Labovitz, MD, St. Louis University Hospital, 1325 South Grand Boulevard, St. Louis, Missouri 63104.

Methods

Patients: The patient population consisted of 51 consecutive patients (30 women, 21 men) with an echocardiographic diagnosis of MAC. They were 54 to 91 years old (mean 70). Patients with calcified mitral valve leaflets were excluded. Most patients were referred for symptoms of chest pain, congestive heart failure, dyspnea or evaluation of a cardiac murmur. Ten patients had hypertension, 7 had coronary artery disease, 4 had had aortic valve replacement, 2 patients had aortic stenosis, 1 patient had cardiomyopathy, and 3 had chronic renal failure. The other patients had no associated detectable cardiovascular abnormalities. The frequency of associated cardiovascular abnormalities were similar in patients with and those without MR.

Echocardiographic studies: M-mode and 2-dimensional (2-D) echocardiography and cardiac Doppler studies were performed using an Irex System IIIB. This phased-array imaging system uses a 2.5-MHz transducer for M-mode and 2-D echocardiography. MAC was diagnosed by echocardiographic findings (Fig. 1) using standard criteria.[1,2,4,20] Measurements of left atrial size were determined from the M-mode study according to recommendations of the American Society of Echocardiography.

Doppler studies: The Doppler unit uses a frequency of 2.0 MHz and can be operated either in a pulsed or continuous-wave mode. In the pulsed mode the sample volume is 7 mm in diameter and can be located at various depths between 0 and 13 cm, the location of which is indicated by a box displayed along the Doppler cursor. The maximal velocity limit



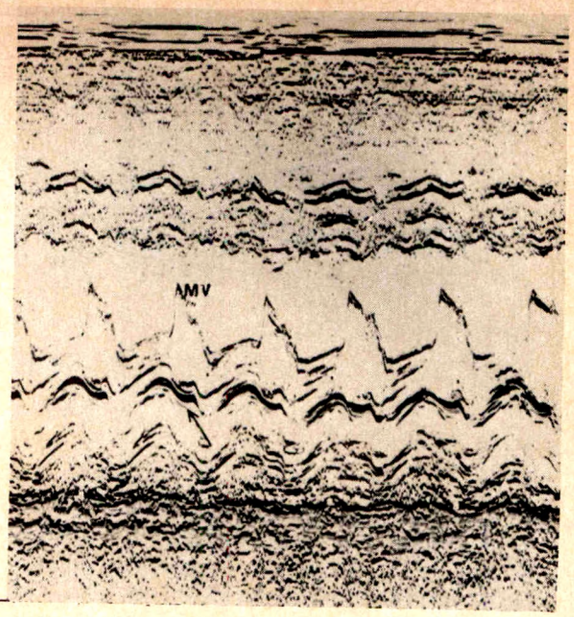
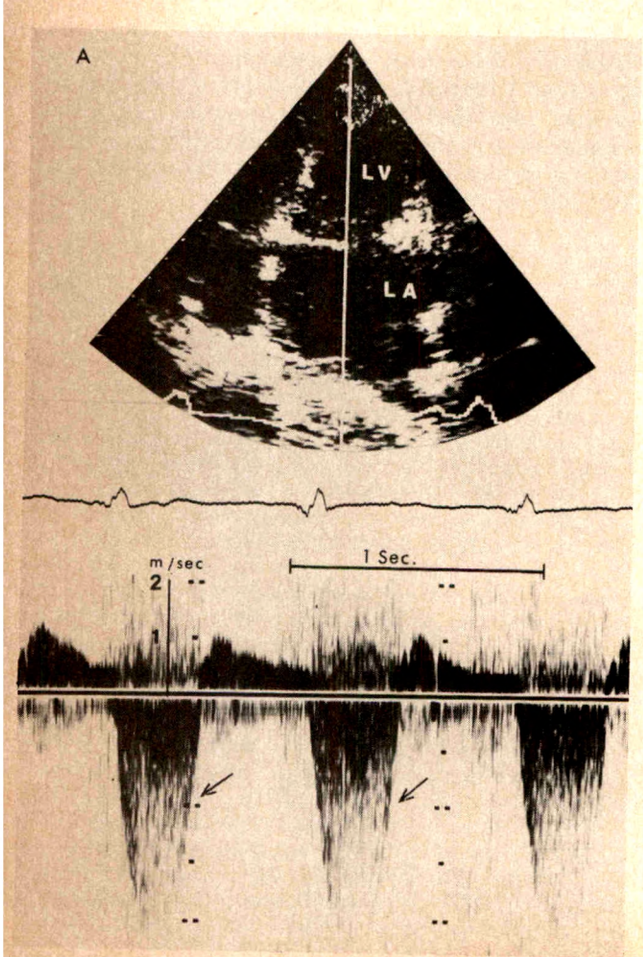


FIGURE 1. M-mode and 2-dimensional echocardiogram from a patient with posterior mitral anular calcification (**arrows**). Bright echoes are seen anterior to the left ventricular posterior wall and move parallel to this structure. LA = left atrium; LV = left ventricle; MV = mitral valve.



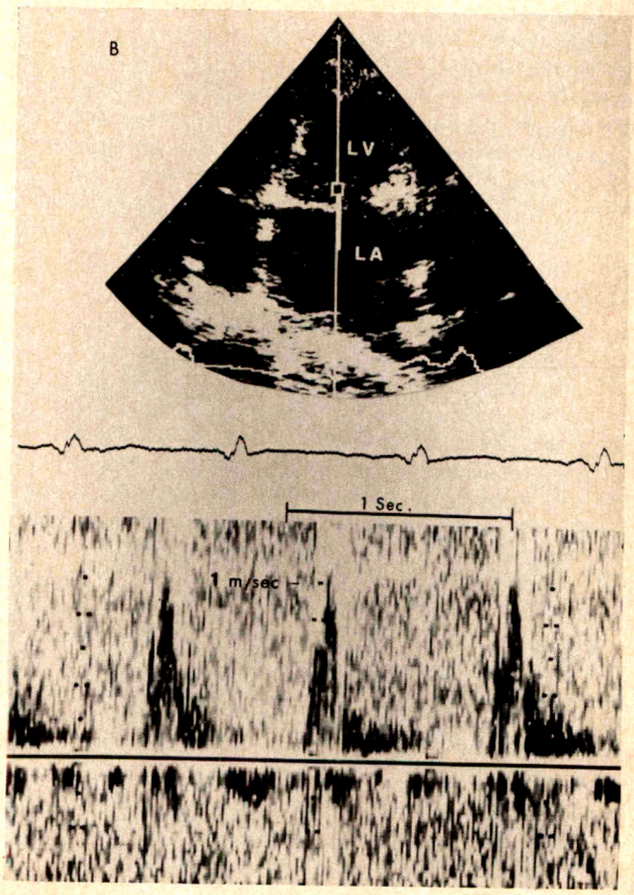


FIGURE 2. Mapping technique for quantitating mitral regurgitation. **A**, with the transducer located at the cardiac apex, transmitral flow is sampled in the continuous mode. **Arrow** indicates high-velocity systolic jet of mitral regurgitation. Forward diastolic flow is recorded above the baseline. Transmitral flow is then sampled in the pulsed mode with the sample volume (as indicated by **box** on the 2-dimensional image) positioned at the mitral valve level (**B**) and at various depths in the left atrium (LA) (**C** and **D**, on opposite page) to sample for regurgitant flow (**arrows**), which is recorded during systole below the baseline. Regurgitant flow detected more than 2 cm behind the mitral valve was graded moderate to severe. This patient has moderate to severe mitral regurgitation. Note the marked left atrial enlargement. LV = left ventricle.

using a baseline offset is 3.4 m/s at depths of less than 8 cm and 2.2 m/s at depths of 8 to 13 cm. The continuous-wave Doppler mode permits recording of velocities of up to 6 m/s, although range resolution is no longer possible as Doppler shifts are detected along the entire Doppler beam. The blood flow velocities can then be displayed graphically as a spectral analysis on hard copy, with the gray scale of the spectral analysis proportional to the number of red blood cells moving at any given velocity.

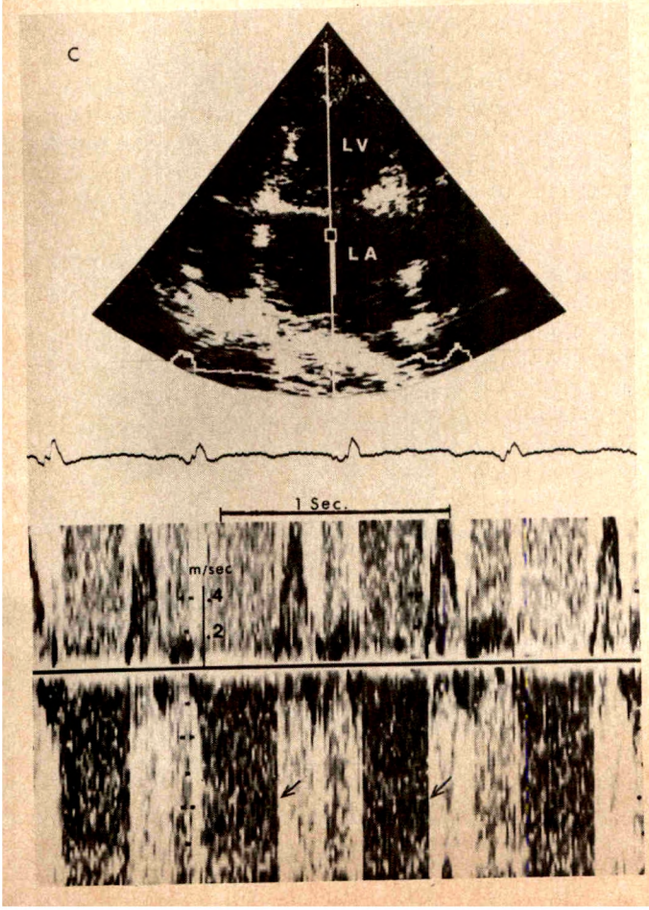
Transmitral flow was sampled by placing the transducer at the cardiac apex and aligning the Doppler cursor parallel to flow using the 2-D image from the 4-chamber view. The valve was routinely scanned first in the continuous mode to determine maximal velocities of left ventricular inflow as well as to detect the presence of MR. MR was defined as a holosystolic jet moving away from the transducer with velocity of more than 2 m/s. If MR was present, it was quantitated in the pulsed mode and the extent of the regurgitant jet was mapped in the left atrium. For the purposes of this study, systolic flow away from the transducer seen 2 cm or more into the left atrium was considered significant (moderate to severe) MR (Fig. 2). Jets that were less than 2 cm into the left atrium were considered mild MR. The mitral valve orifice area was determined by the pressure half-time method[14]; valve areas less than 2 cm^2 were classified as functional MS (Fig. 3).

Patient groups: The patients were separated into 4 groups on the basis of Doppler findings. Group I consisted of patients with essentially normal mitral flow dynamics and no evidence of MS or MR, group II of patients with mild MR, group III of patients with moderate-to-severe MR, group IV consisted of patients with obstruction to left ventricular inflow (MS).

Statistical analysis: To compare echocardiographic and Doppler variables among the 4 groups, a 1-way analysis of variance was used. Intergroup analyses were performed using a Tukey's test. Chi-square analysis was used to determine significant differences ($p < 0.05$) between clinical characteristics in patients with and those without significant MR.

Results

Clinical characteristics: Of the 51 patients, 28 (55%) had MR diagnosed by Doppler. Of these 28 patients, an apical systolic murmur was heard in only 17 (61%). Of the 17 patients found to have moderate to severe MR by Doppler, only 65% had a murmur consistent with MR. Eleven of the 23 patients without evidence of MR by Doppler had a systolic murmur. An apical systolic murmur, therefore, had limited predictive value in screening patients with MAC for MR. When the patients with minimal or no MR (groups I and II) were compared to those with moderate to severe MR (group III), no statistically significant differences in symptoms and clinical findings were noted; however, a systolic murmur, dyspnea and a history of congestive heart failure were found more frequently in the patients who had moderate to severe MR (Table I). Of the 4 patients found to have MS by Doppler echocardiography, none had a diastolic rumble or opening snap, 2 had a systolic ejection murmur loudest at the left sternal



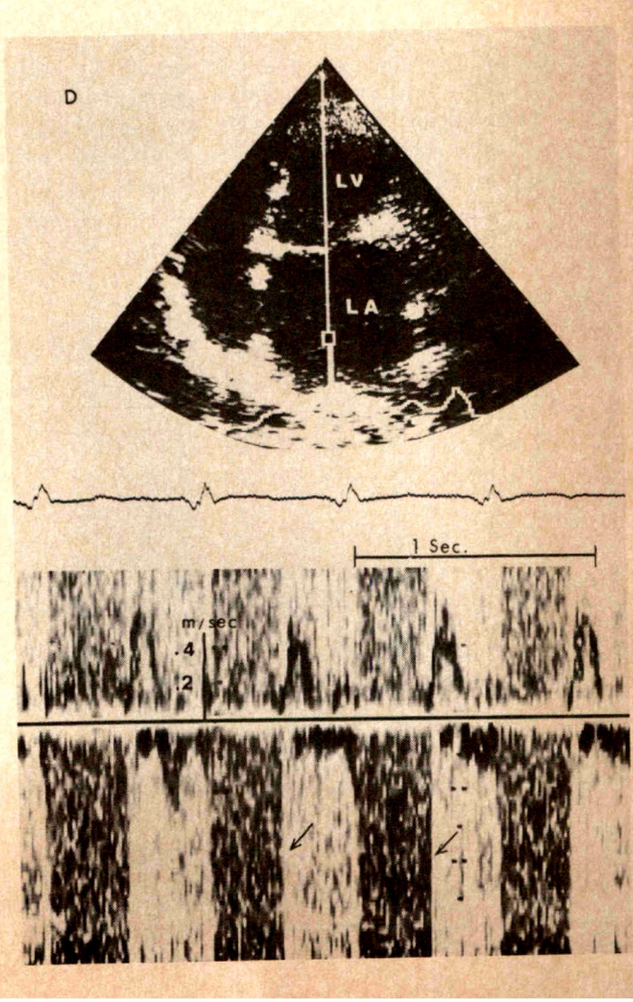


TABLE I Clinical Characteristics of Patients with Doppler Quantitated Mitral Regurgitation

	No or Mild MR Groups I and II	Moderate to Severe MR Group III	p
n	30	17	...
Apical systolic murmur	50%	65%	NS
Chest pain or CAD	33%	41%	NS
Dyspnea	23%	35%	NS
CHF	20%	41%	NS
Age (yr)			
Mean	70	71	NS
Range	54–91	57–88	...

CAD = coronary artery disease; CHF = congestive heart failure; MR = mitral regurgitation; NS = not significant.

border, 3 had symptoms of congestive heart failure, and 1 was status post–cardiac arrest.

Echocardiographic and Doppler studies: The 51 patients were classified into 4 groups on the basis of Doppler examination. Group I included 19 patients (37%) who had no MR or MS, group II included 11 patients (22%) who had mild MR, group III included 17 patients (33%) who had moderate to severe MR, and group IV included 4 patients (8%) who had functional obstruction to left ventricular inflow (MS).

A statistical analysis of echocardiographic and Doppler parameters in the 4 groups is illustrated in Table II. The patients with moderate to severe MR (group III) had a significantly larger mean left atrial size (4.95 ± 0.74 cm) compared with group I (4.18 ± 0.75 cm) and group II (4.28 ± 0.44 cm). There was no statistically significant difference in left atrial size between patients with minimal or absent MR. Peak velocity of left ventricular filling was significantly higher in group IV patients (1.75 ± 0.33) than in group I (1.21 ± 0.28), group II (1.38 ± 0.35) and group III (1.21 ± 0.25) patients. The mitral valve orifice as measured by the Doppler pressure half-time method was significantly smaller in patients with MS (group IV) (1.67 ± 0.26) compared to group I (3.10 ± 0.64), group II (3.35 ± 1.15) and group III (3.18 ± 0.72). Therefore, significant left atrial enlargement in a patient with normal left ventricular inflow velocities and relatively normal mitral valve orifice was a good predictor of moderate to severe MR.

Functional mitral stenosis: Four patients had Doppler-defined MS. Two of these 4 patients underwent right- and left-sided cardiac catheterization, at which time obstruction to left ventricular inflow was confirmed. The clinical and laboratory characteristics of these patients are listed in Table III. In general, these 4 patients had much denser MAC and 3 of the 4 had anterior as well as posterior anular calcification seen on echocardiography. All 4 patients had evidence of at least some calcification of the aortic root and valve while 2 patients were believed to have hemodynamically significant aortic stenosis. All 4 patients had symptoms referable to the cardiovascular system.

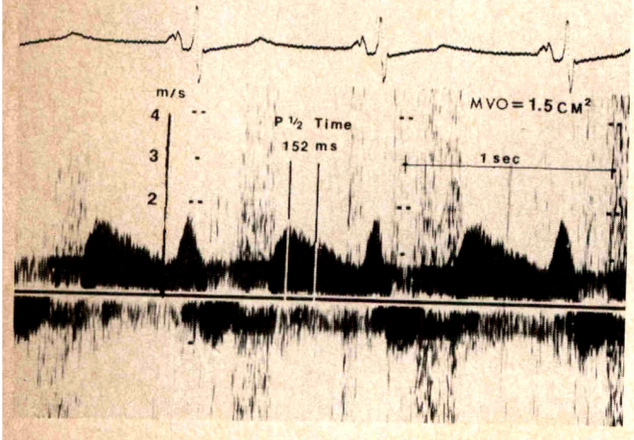


FIGURE 3. Pressure (P) half-time technique for calculation of mitral valve orifice (MVO). The pressure half-time is the time required for the pressure gradient to fall to half its peak value. Because of the squared relation between velocity and gradient, this is the time required for the peak velocity to decrease to a value equal to the peak velocity divided by the square root of 2. An estimate of mitral valve orifice is then obtained by dividing 220 ms by this number. In this patient, mitral valve orifice equals 220/152 or 1.5 cm^2.

Discussion

In 1962, Korn et al[21] reported a morphologic study of 14 patients with massive MAC where they found a complete rigid ring of calcification 1 to 3 cm in diameter in the region of the mitral anulus. In 9 of the 14 patients a significant degree of stenosis, as judged by visual inspection, was present in the absence of leaflet disease. Since then, other investigators[22–24] have reported invasive hemodynamic confirmation of such lesions at cardiac catheterization. In all cases, physical findings suggestive of MS were lacking. However, no consecutive series estimating the incidence of left ventricular inflow obstruction in patients with MAC has been reported because of the lack of a sensitive noninvasive method to describe this phenomena.

Doppler ultrasound provides good correlation when compared with invasive technique and 2-dimensional echocardiography in estimation of mitral valve orifice when the pressure half-time technique reported by Hatle et al is applied.[14,15,25] Since this technique depends on flow dynamics between left atrium and left ventricle, one would expect this relation to accurately reflect valve orifice in the presence of subvalvular and valvular stenosis.

Several investigators have examined the usefulness of Doppler in the evaluation of MR.[16–19] The specificity of this technique ranged from 89 to 100% and the sensitivity was 90% or greater compared with angiography. Mild cases of MR at left ventriculography are frequently missed by Doppler. Using a mapping technique similar to that used in the present study, Abbasi et al[16] showed a high correlation (r = 0.88) compared to ventriculography when assessing the degree of regurgitation.

MAC is frequently believed to be a benign degenerative process that affects the elderly. However, in the present study, 33% of the patients with MAC had valvular insufficiency of hemodynamic importance as graded by Doppler. In addition, a few patients have

TABLE II Echocardiographic and Doppler Findings

	I No MR/MS	II Mild MR	III Moderate to Severe MR	IV MS
n (%)	19 (37%)	11 (22%)	17 (33%)	4 (8%)*
Apical systolic murmur (%)	47	55	65	50
Left atrial size (cm)	4.18 ± 0.75	4.28 ± 0.44	4.95 ± 0.74*	4.90 ± 0.93†
Peak velocity (m/s)	1.21 ± 0.28	1.38 ± 0.35	1.21 ± 0.25	1.75 ± 0.33*
MV orifice (cm^2)	3.10 ± 0.64	3.35 ± 1.15	3.18 ± 0.72	1.67 ± 0.26*

* $p < 0.05$ vs group I; † $p < 0.06$ vs group I.
MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve.

TABLE III Four Patients with Mitral Anular Calcification and Functional Mitral Stenosis

Sex & Age (yr)	Murmur	Left Atrial Size (cm)	Peak Velocity (m/s)	Doppler MV Orifice (cm^2)	Cath MV Orifice (cm^2)
M73	IV/VI HSM	4.0	2.2	1.9	—
F70	III/VI SEM	5.7	1.8	1.5	1.2
F78	III/VI SEM	5.7	1.5	1.4	—
F67	III/VI SEM	4.2	1.5	1.9	2.2

HSM = holosystolic murmur; MV = mitral valve; SEM = systolic ejection murmur.

functional MS even after patients with abnormally thickened or calcified mitral valve leaflets were excluded from consideration.

Although patients referred for echocardiographic examination represent a select group, the demographic features of our study patients are similar with respect to age, physical findings and symptoms compared with other series selected by echocardiographic, roentgenographically or autopsy proved MAC.[3,9–11,13] A systolic murmur heard at the left sternal border or apex has been reported in 35 to 100%[7,9,10,12,13] of patients with MAC, compared with approximately 60% in the present study. However, MR is not believed to be the cause of this murmur in all of these patients.[7,8,10,20] Other explanations for the murmur include the vibration of the mitral valve ring itself or systolic ejection murmurs transmitted from a sclerotic aortic root.[10–12] Decreased mobility of the mitral valve and chordae as well as loss of the normal systolic "sphincter" action of the mitral ring are believed to be responsible for the valvular insufficiency. Simon and Liu[10] suggest from their report of 59 postmortem examinations of cases of MAC that significant MR is a common occurrence in the presence of this lesion. Mellino et al[8] found MR in 10 of 24 (42%) patients with MAC undergoing cardiac catheterization.

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Mitral Valve Prolapse and Ruptured Chordae Tendineae

ROBERT M. JERESATY, MD, JESSE E. EDWARDS, MD,
and SURENDRA K. CHAWLA, MD

To determine the causes of ruptured chordae tendineae and a suspected etiologic role for mitral valve prolapse (MVP), the mitral valve in 25 consecutive and surgically proved cases of chordal rupture were examined. The diagnosis of MVP was made on the basis of redundancy and marked hooding of the mitral leaflets and on histologic changes. MVP was the underlying morphologic abnormality in 23 patients, only 1 of whom had infective endocarditis that was responsible for the rupture. Thus MVP was the only underlying morphologic abnormality in 22 of 25 patients (88%). Another finding in this study was the demonstration of auscultatory and angiographic or echocardiographic evidence of MVP in 4 patients, aged 4 to 11 years (mean 7), before chordal rupture; no patient had had endocarditis. The morphologic and historical evidence would indicate that MVP is probably the most common cause of so-called spontaneous chordal rupture.

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Mitral valve prolapse (MVP) generates considerable interest in view of its prevalence, its variable symptoms, its auscultatory findings and its complications.[1–3] Some investigators believe that this syndrome is the underlying cause of ruptured chordae tendineae of the mitral valve[3–8]; others do not.[9–11] To determine the causes of ruptured chordae tendineae and a suspected etiologic role for MVP, we examined the mitral valve and reviewed clinical, echocardiographic and cineangiographic findings in 25 consecutive cases of surgically proved chordal rupture. In 4 of the patients, MVP had been documented 4 to 11 years earlier, adding further support to the suspected causal relation.

Methods

The surgical pathologic series: In addition to gross examination by the cardiac surgeon, the cardiologist and the Pathology Department at Saint Francis Hospital and Medical Center, 20 of the 25 valves were examined by one of us, 2 by the Department of Pathology at Brigham and Womens Hospital in Boston, and 1 by William C. Roberts in Bethesda. To distinguish ruptured chordae tendineae from chordae that had been cut during the surgical procedure, the pathologist was aided by the surgeon's having placed a metal clip across the base of chordae that had been found ruptured at operation. All of our 25 patients, except 1 who underwent surgery in July 1977, underwent mitral valve replacement for severe mitral regurgitation (23 at Saint Francis Hospital and Medical Center and 2 elsewhere) during a 4½ year period starting in June 1978.

The diagnosis of MVP was made on the basis of the following findings[7,12,13]: (1) large, redundant leaflets; (2) marked interchordal hooding involving at least half of the anterior leaflet or at least two-thirds of the posterior leaflets; (3) large mitral anulus, seen in 15 of 25 of our cases, which was larger than 10.5 cm (the upper limit of normal[13]) (mean 12.7, range 10.5 to 16.5); and (4) microscopic evidence of myxomatous changes in the form of thickening of the spongiosa invading and focally interrupting the fibrosa.

Documentation of mitral valve prolapse before chordal rupture—4 patients: In 4 patients, the diagnosis of MVP was made before the occurrence of chordal rupture. The clinical diagnosis of MVP was made on the basis of a nonejection click often associated with a late systolic murmur.[1–3] The M-mode echocardiographic and angiographic criteria were those previously described.[3] The M-mode criteria for ruptured chordae tendineae were those summarized by Child et al[14] and the 2-dimensional echocardiographic criteria were those described by Mintz et al.[15]

Results

Clinical, echocardiographic, hemodynamic and angiographic data: Of the 25 patients with surgically proved ruptured chordae tendineae, 16 were men and 9 were women, aged 28 to 84 years (mean 61). Only 1 patient gave a history of rheumatic fever. A systolic murmur was noted 3 to 45 years before surgery in 21 of the 23 patients in whom information on previous murmurs was available; in 1 patient, no murmur was heard before recent deterioration, during which a loud pan-

From the Section of Cardiology, Department of Medicine, Saint Francis Hospital and Medical Center, Hartford, Connecticut. Manuscript received June 11, 1984; revised manuscript received August 31, 1984, accepted September 4, 1984.

Address for reprints: Robert M. Jeresaty, MD, Director, Section of Cardiology, Saint Francis Hospital and Medical Center, 114 Woodland Street, Hartford, Connecticut 06105.

systolic murmur was noted, and in another patient, no murmur was noted 3 years before recent deterioration. Information on the type of murmur was usually lacking. However, in 5 patients, including 1 who had endocarditis, the murmur was late systolic and preceded by a click in 3, and in 5 other patients the murmur was pansystolic. In all 25 patients, a pansystolic murmur was heard before mitral valve replacement.

A history of sudden clinical deterioration was obtained in 15 patients and in the remaining patients, heart failure was insidious in its onset and in its course. As will be mentioned later, there was a history of endocarditis in only 3 patients, and in 2 of these, endocarditis was believed to be responsible for the chordal rupture.

An M-mode echocardiogram of good quality was available for our review in 20 patients. Coarse diastolic fluttering of the posterior leaflet, which was observed in 12 patients, was the most common finding. Systolic echoes in the left atrium were noted in 9 patients and systolic fluttering of the mitral valve in 5. A 2-dimensional echocardiogram was available in only 5 patients, confirming the M-mode diagnosis of ruptured chordae tendineae without providing additional diagnostic information.

The pulmonary artery wedge pressure tracing showed a prominent "v" wave in 18 of our patients. Cine left ventriculography showed severe mitral insufficiency in all patients with evidence of MVP in 21. Aortic insufficiency was found in 2. Coronary arteriography, which was performed in 23, was normal in 17 and showed coronary artery disease in 6 (1-vessel disease with 70% or less stenosis in 4 and 2-vessel disease in 2).

Mitral valve replacement with a porcine heterograft was carried out in all patients, aortic valve replacement in 2, closure of an atrial septal defect in 1 patient and coronary artery bypass surgery in 5. Only 1 patient died postoperatively.

Pathologic findings: MVP was the underlying pathologic abnormality in 23 patients (15 men and 8 women), bacterial endocarditis in the absence of MVP in 1 patient with tetralogy of Fallot, and the cause of the mitral valve disease was not evident in an 81-year-old woman. Of the 23 patients with underlying MVP, 2 have had endocarditis that could be held historically and pathologically responsible for the rupture in only 1 patient; in the other patient, a pansystolic murmur had been heard and an M-mode echocardiogram had shown evidence of chordal rupture before the occurrence of endocarditis. Thus, in our series, endocarditis occurred in 3 patients, including 2 with MVP, but was the cause of rupture in only 2. Excluding these 2 patients and the patient in whom MVP was not noted and the underlying pathology had not been defined, MVP was the only underlying pathologic abnormality in 22 of our 25 patients (88%) who had ruptured chordae tendineae (Table I).

TABLE I Cause of Ruptured Chordae in 25 Patients

MVP without endocarditis	22 (88%)
MVP with endocarditis	1 (4%)
Endocarditis without MVP	1 (4%)
Undetermined	1 (4%)

MVP = mitral valve prolapse.

The ruptured chordae were those of the posterior leaflet in 13 patients (52%), of the anterior leaflet in 10 (40%) and of both in 2 (8%). Of the chordae attached to the posterior leaflet, those of the middle scallop were the most commonly ruptured (11 of 13). In all of our patients, the characteristic hooding was not limited to the segment of the valve attached to the ruptured chordae.

The typical gross specimen was a valve that had been removed in 1 piece and opened at or near 1 of the commissures. In an occasional case, continuity of the valvular elements had been retained so that the orifice was intact (Fig. 1). In all specimens, there were varying degrees of interchordal hooding (Fig. 2). In no instances was there evidence of commissural fusion.

In all cases, histologic examination revealed that there were some signs characteristic of the myxomatous mitral valve. Among the chords that had ruptured, changes varied. The most consistent change was loss of clear, collagenous staining with the van Gieson counterstain done on sections stained primarily for elastic tissue. In some, there was a fragmentation of the distal end with little fibrous reaction. Occasionally a fibrous reaction

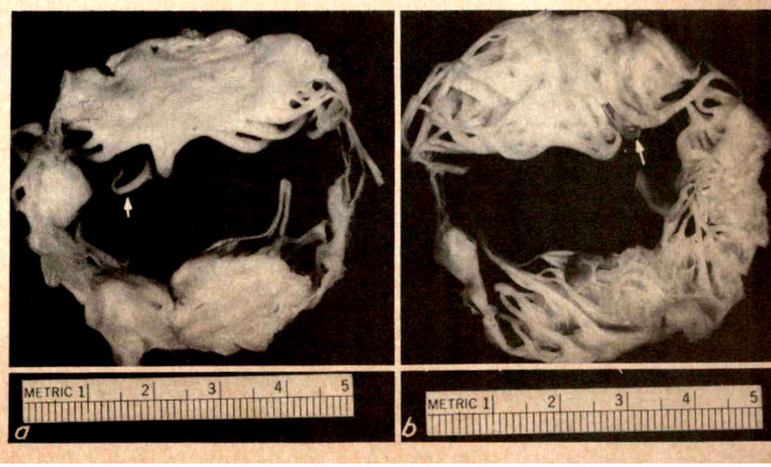

FIGURE 1. (R-79-160, case 6, male, age 51 years). Continuity of valvular elements has been maintained. **a,** valve viewed from atrial aspect. Anterior leaflet in **upper** part of photograph. Valvular elements vary in thickness. Greatest opacity in anterior leaflets of which inserting chordae had ruptures as shown in **b. b,** ventricular aspect of valve. Metal clip across base of ruptured chordae which inserts into anterior leaflet (**arrows**).

TABLE II Mitral Valve Prolapse Diagnosed Before Chordal Rupture in 4 Patients (Mean 7 Years)

No. of Pts.	Findings
2	MSC, LSM No echo or cine
1	MSC, LSM Positive cine
1	LSM Positive echo & cine

LSM = late systolic murmur; MSC = midsystolic click.

occurred at the distal end imparting a knobby thickening at the extremity.

Mitral valve prolapse documented before chordal rupture: subseries of 4 patients (Table II): In 4 patients, MVP was documented 4 to 11 years (mean 7) before chordal rupture, which was associated with clinical deterioration and a new pansystolic murmur. No patient had had endocarditis. In 3 of these patients, a midsystolic click followed by a late systolic murmur had been heard and the cine left ventriculogram, which was performed in 1, had been positive for MVP. The phonocardiogram of 1 of these 3 patients, which has been previously published,[3] showed a midsystolic click followed by a late systolic murmur with subsequent development of a new pansystolic murmur associated with acute heart failure; suspected MVP and chordal rupture were subsequently confirmed at surgery. The fourth patient had a late systolic murmur and a positive echocardiogram and cineangiogram in 1971 (Fig. 3); his chordal rupture occurred probably while he was chopping wood in 1979. His preoperative phonocardiogram, echocardiogram and cine left ventriculogram are shown in Figure 4 and his mitral valve is shown in Figure 1.

Discussion

MVP has been recognized during the past 2 decades as the most prevalent mitral valve disorder and the most frequent cause of chronic pure mitral insufficiency.[3,8,13] Although the association of MVP and chordal rupture has been frequently reported, the etiologic link between them has been refuted by some workers[9–11] but recognized or postulated by others.[3–8] The first report of ruptured chordae associated with probable MVP appeared in 1966.[16] Despite this report, the cause of ruptured chordae tendineae has been ascribed by most investigators to other diseases[10,17,18] and most cases have been labeled as "idiopathic."[10] In 1972, Selzer et al[9] stated that "etiologically there is no relationship or overlap between isolated rupture of chordae tendineae and 'the billowing mitral leaflet syndrome.' " He also stated in another report[10] that the most common cause of rupture of chordae tendineae in the course of MVP is infective endocarditis and that spontaneous rupture of chordae tendineae in milder cases of MVP is "unproven and doubtful." He cited several arguments against a causal association between MVP and chordal rupture: (1) Ruptured chordae usually affects males over the age of 45 years. (2) The holosystolic murmur appears abruptly and is not preceded by clinical findings of prolapsing mitral valve. (3) Rupture of chordae tendineae in a patient with MVP is rare and in many

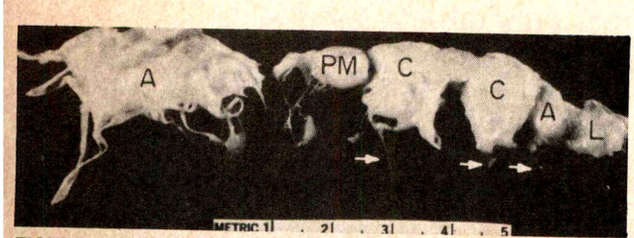

FIGURE 2. (R-80-251, case 3, female, age 66 years). A case in which continuity of valvular tissue had been divided. The anterior (A) leaflet shows relatively little change. The 3 scallops of the posterior leaflet are prominent. Each scallop of the posterior leaflet displays prolapse or hooding, whereas the central of the scallops is bifid. Chordae to central and anterolateral scallops had ruptured (**arrows**). AL = anterolateral scallop; C = central scallop; PM = posteromedial scallop.

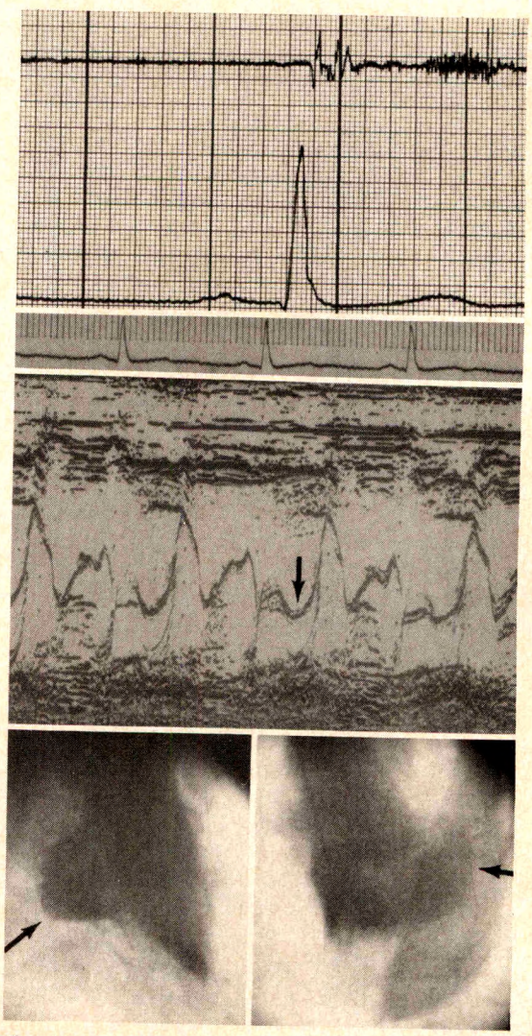

FIGURE 3. Case 6. Phonocardiogram, echocardiogram and cine left ventriculogram documenting MVP in 1971 in a 51-year-old man who had ruptured chordae tendineae while chopping wood in 1979 (see Figure 4 for same studies after chordal rupture and Figure 1 for pathologic documentation of MVP and chordal rupture). Reproduced with permission of Raven Press from Jeresaty.[3]

cases can be traced to endocarditis rather than being spontaneous. (4) The areas of the mitral valve detached from the chordae may show myxomatous changes, but these changes are secondary and are related to the trauma of turbulent flow, the remainder of the cusp being normal.

These well formulated and cogent arguments have influenced us in the design of our study. We examined 25 consecutive patients, looking for historical and pathologic evidence of endocarditis as the cause of rupture and seeking evidence of a primary MVP as a possible etiologic mechanism of the rupture. Furthermore, we reviewed the physical and echocardiographic findings in 4 patients with surgically proved chordal rupture who had been evaluated by us a mean of 7 years earlier.

We concur with Selzer that despite the preponderance of MVP in women, most patients with ruptured chordae tendineae are men older than age 45 years (15 of our 25 patients, 60%). This finding may simply indicate that men with MVP are at a higher risk of having ruptured chordae tendineae as they are of having progressive mitral insufficiency.

One of the major findings of our study was the clinical demonstration of MVP in 4 patients who, in the absence of endocarditis, subsequently had ruptured chordae tendineae (Table II). These 4 patients, when added to 11 others with previously documented MVP[5,11,19–25] (midsystolic and late systolic murmur in 8, isolated late systolic murmur in 3 with a positive echocardiogram in 2) and subsequent chordal rupture in the absence of endocarditis, provide a strong argument in favor of a causal relation between MVP and ruptured chordae tendineae. In most patients with ruptured chordae tendineae, a preceding click and a soft late systolic murmur may have been overlooked by physicians who, before 1960, considered these findings to be extracardiac.[3,11] It is also possible that no adequate auscultation was performed and no echocardiogram was obtained before the appearance of a pansystolic murmur of chordal rupture.[11]

In our series, MVP was the underlying pathologic abnormality in 23 patients (92%), endocarditis in the absence of MVP in 1 patient, and the valvular abnormality was unknown in 1 patient. Of the 23 patients with underlying MVP, 2 have had endocarditis, but it is only in 1 patient that endocarditis could be held historically and pathologically responsible for the chordal rupture. Therefore, our series demonstrates that MVP, per se, is the underlying cause of ruptured chordae tendineae in 88% of our patients and that endocarditis is responsible for only 8%, including only 4% of chordal rupture in patients with MVP (Table I), Selzer's statement notwithstanding.[10] An association of MVP and proved myxomatous mitral valve (necropsy or surgery) has also been reported.[3,11,13,19,21,22,24–31]

Demonstration in our series and in others[6,7] of gross and histologic changes of MVP in parts of the mitral valve not involved in chordal rupture adds further confirmation to the postulated causal link between MVP and rupture. Moreover, friction lesions of the left ventricular endocardium frequently noted in idiopathic MVP have been observed in relation to the chordae that have ruptured, lending support to the concept that the usual features of MVP existed before the event of chordal rupture.[6]

Rupture of chordae to the anterior leaflet is not uncommon; it occurred in 12 of our patients, including 2 with additional posterior leaflet rupture. The clinical picture of these patients was indistinguishable from those with ruptured chordae to the posterior leaflet. When the posterior leaflet was involved, the chordae to the middle scallop were the most frequently affected (11 of 13 patients).[32] Unlike Waller et al,[13] we have noted a large mitral anulus in most of our patients with MVP and ruptured chordae tendineae (15 of 23).

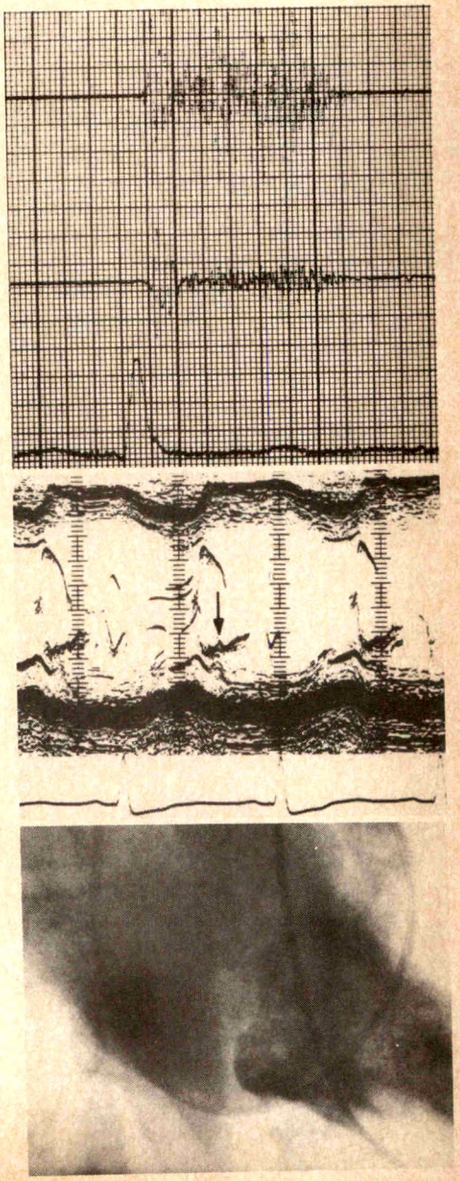

FIGURE 4. Case 6. Phonocardiogram (pansystolic murmur), echocardiogram (coarse diastolic fluttering [**arrow**]), and cine left ventriculogram (mitral valve prolapse and marked mitral regurgitation) repeated in same patient as in Figure 3 eight years later, after chordal rupture (see Figures 1 and 3).

In reviewing our 25 cases, we noted a new echocardiographic sign, i.e., coarse diastolic fluttering of the posterior leaflet as the transducer was angled toward the apex of the left ventricle below the mitral valve.[33] We also noted on cine left ventriculography in the right anterior oblique projection a late diastolic fluttering of the thickened mitral leaflet.[33] These echocardiographic and angiographic findings will be published separately.

Chordal rupture in MVP may be due to increased tension resulting from the enlarged area of the cusp[34] and to degeneration of collagen within the central core of the chordae.[27]

Carpentier et al[26] described the "pellucid" or fibroelastic mitral valve as a separate pathologic entity frequently associated with chordal rupture. Unfortunately, we have not recognized the pathologic changes described by these investigators.

Chordal rupture should be added to the list of complications that may interrupt the general benign course of MVP. Although we have not examined all of our first 100 patients with MVP seen before 1972 and described in 1973,[2] we have follow-up evaluation on most of these patients: Two of our patients with ruptured chordae tendineae belong to this group of patients yielding an incidence of chordal rupture of at least 2% over a 13-year follow-up period. Admittedly, our patients represent a selected group of patients referred to a cardiology service, and the incidence of ruptured chordae may be smaller in an unselected group of patients with MVP. Considering the prevalence of MVP that affects 5 to 6% of the population, the risk of any patient with this syndrome having chordal rupture is small.[3] However, MVP is the most frequent cause of ruptured chordae tendineae and, therfore, the term "idiopathic" should no longer be used to designate most cases of ruptured chordae tendineae.[10]

Acknowledgment: We acknowledge the cooperation of the full-time and practicing cardiologists of Saint Francis Hospital and Medical Center, whose cases have been incorporated in this study. The secretarial assistance of Dorothea Murray is greatly appreciated.

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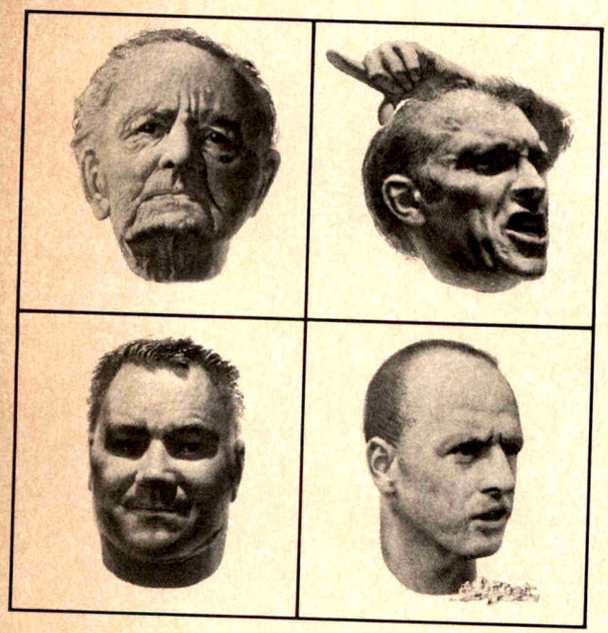

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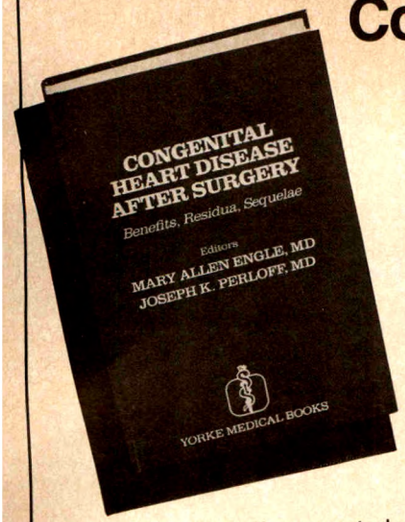

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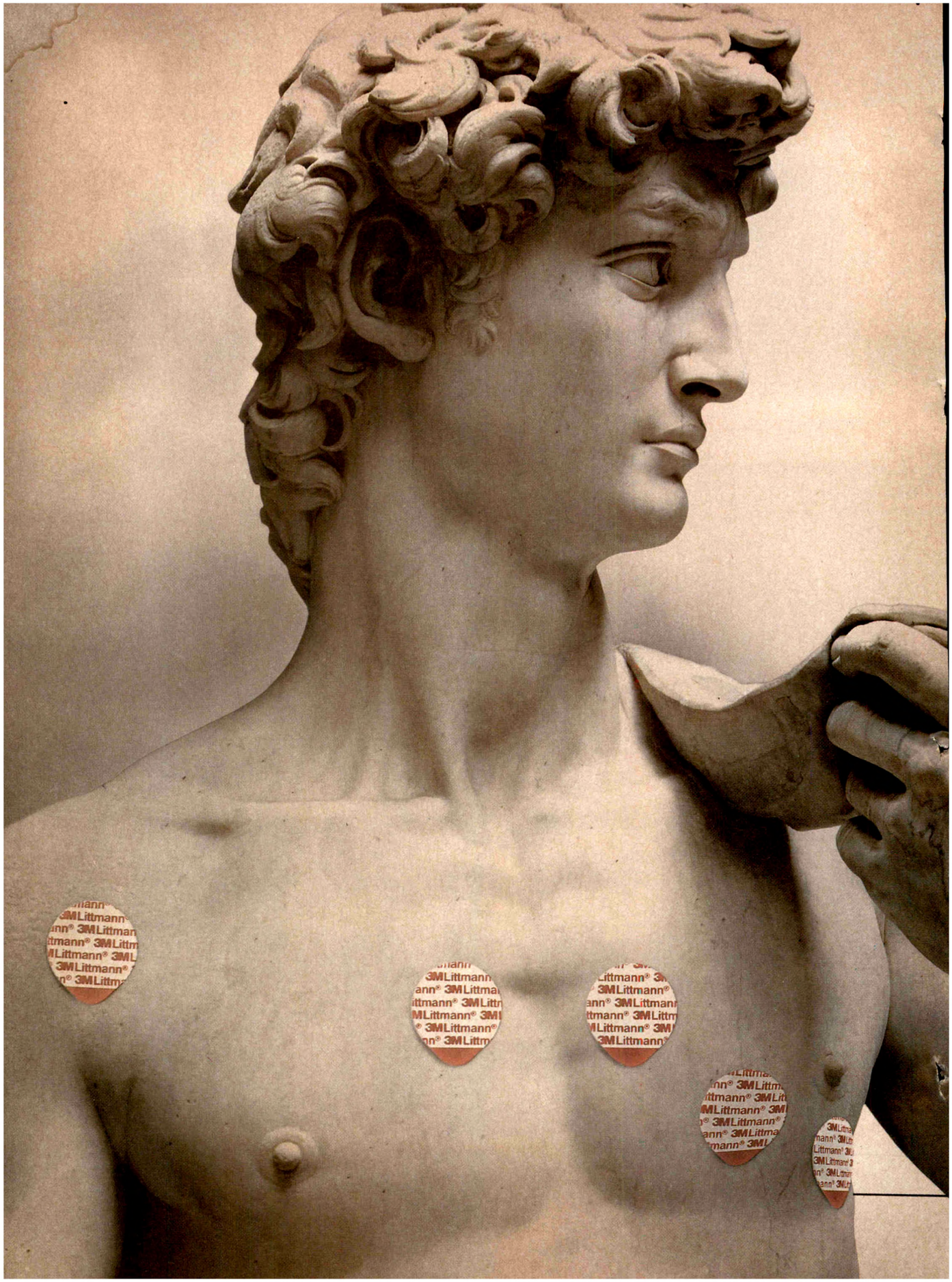
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Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/ kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

Body System/ Adverse Reaction	Total (Volunteered and Elicited) Visken (pindolol) (N = 322) %	Active controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	< 1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	< 1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	< 1	0
Rash	2	3	3

* Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

More than 7 million patient-years of experience

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and non-thrombocytopenic purpura.

Gastrointenstinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥ 80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 5 mg b.i.d. alone or in combination with other antihypertensive agents. An antihypertensive response usually occurs within the first week of treatment. Maximal response, however, may take as long as or occasionally longer than two weeks. If a satisfactory reduction in blood pressure does not occur within 3-4 weeks, the dose may be adjusted in increments of 10 mg per day at these intervals up to a maximum of 60 mg per day.

HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05).

[VIS-Z3 6/15/83]

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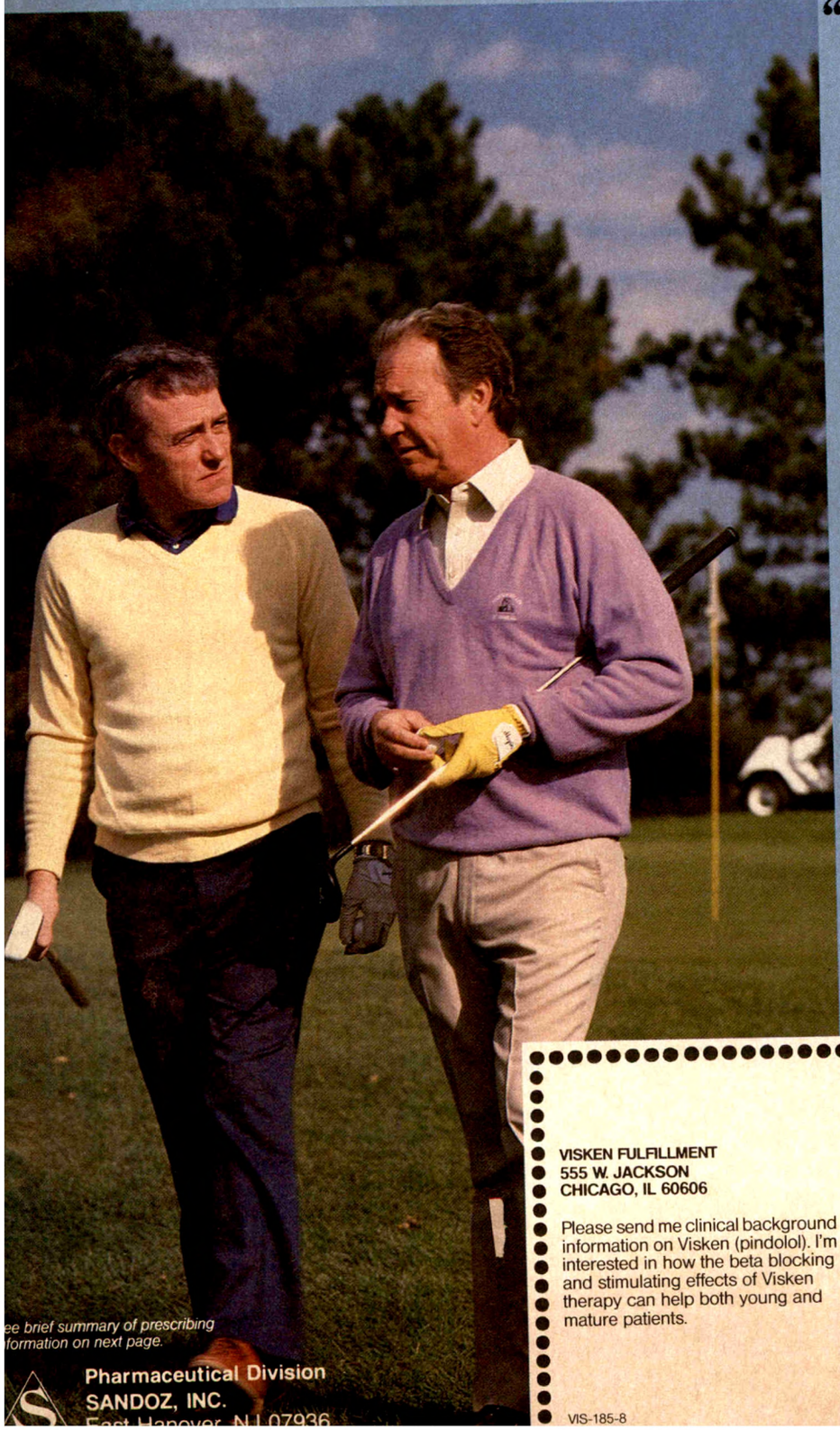
Visken®
(pindolol)
A different kind of beta blocker

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

"What makes Visken® (pindolol) different?"



"Unlike most beta blockers, Visken (pindolol) is the beta-active agent with dual action."

When you're asked about Visken therapy, you'll want to have the answers.

ee brief summary of prescribing formation on next page.

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

VISKEN FULFILLMENT
555 W. JACKSON
CHICAGO, IL 60606

Please send me clinical background information on Visken (pindolol). I'm interested in how the beta blocking and stimulating effects of Visken therapy can help both young and mature patients.

VIS-185-8

Visken®
(pindolol) 5-mg and 10-mg Tablets

Send me the answers.

Name _____
(please print)

Address _____

City _____ State _____ ZIP _____

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644-501 Issued: June 1984

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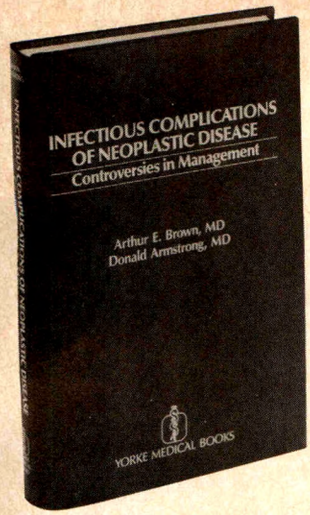

INFECTIOUS COMPLICATIONS OF NEOPLASTIC DISEASE

Controversies in Management

Edited by Arthur E. Brown, MD, and Donald Armstrong, MD
0-914316-43-5, approx. 400 pp., Oct. 1984, $40.00 casebound

About the book

Derived from a symposium sponsored by the Infectious Disease Service, Department of Medicine and the Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York City, and Cornell University Medical College, New York City, this book presents the latest thinking by international authorities, all of whom were invited to present findings in their area of expertise on the diagnosis, treatment, and prevention of various bacterial, fungal, viral, and parasitic infections presenting in patients with neoplastic disease.

This is not just another "proceedings" volume. Rather it is an edited work, with papers by investigators who submitted definitive preparations for publication. Furthermore, the authors take a strong position on their topics, ask probing questions and promote a stimulating forum of controversy.

The result is a concise, dynamic study that belongs in the professional library of every physician treating patients with neoplastic disease.

About the Editors

Arthur E. Brown, MD, is Assistant Attending Physician, Memorial Sloan-Kettering Cancer Center, and Assistant Professor of Medicine and Pediatrics, Cornell University Medical College.

Donald Armstrong, MD, is Attending Physician; Chief of Service; Director, Microbiology Laboratory, Memorial Sloan-Kettering Cancer Center, and Professor of Medicine, Cornell University Medical College

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Immunoprophylaxis and serotherapy of bacterial infections
Immunoprophylaxis of varicella-zoster infections
Current status of prophylaxis of infection with protected environments
Protected environments are discomforting and expensive and do not offer meaningful protection

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Clinical Clues to MIXED ANGINA *No. 1*

Thirty seconds ago he was reading

He wasn't exercising; his myocardial oxygen demand didn't increase. Yet now he's having an angina attack.

That's the unpredictability of MIXED ANGINA—vasoconstriction coexisting with fixed coronary lesion, to produce a critical reduction of myocardial blood flow.

And because vasoconstriction is an unpredictable event, ischemia and pain occur unpredictably:

- at rest, or even during sleep
- at varying levels of exercise
- upon exposure to cold
- under emotional stress
- diurnally, typically in the morning

PROCARDIA® (nifedipine) is a primary therapy for the patient with MIXED ANGINA. It prevents vasoconstriction in both large coronary arteries and coronary arterioles to maintain myocardial blood flow and oxygen supply. At the same time, PROCARDIA dilates peripheral arteries to reduce afterload and myocardial oxygen demand.

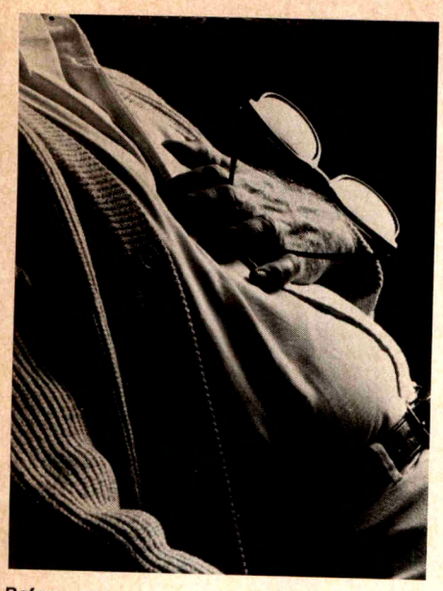
As a result, PROCARDIA can significantly reduce your patient's angina attack rate and need for nitroglycerin!

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Primary Protection in
MIXED ANGINA

Please see PROCARDIA® (nifedipine) brief summary on next page.

Thirty seconds ago he was reading.



PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PRIMARY PROTECTION IN MIXED ANGINA

Usual Effective Dosage: 30 to 60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases.

A Favorable Safety Profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

Reference:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 106:644-652, 1983.

Brief Summary
PROCARDIA® (nifedipine) Capsules
For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA (nifedipine). This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has been demonstrated.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered. However, the relationship to PROCARDIA therapy is uncertain.

When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and placental abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, allergic hepatitis, and gingival hyperplasia. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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LABORATORIES DIVISION
PFIZER INC.

Findings on Endomyocardial Biopsy in Infants and Children with Dilated Cardiomyopathy

ALAN B. LEWIS, MD, HARRY B. NEUSTEIN, MD, MASATO TAKAHASHI, MD, and PAUL R. LURIE, MD

Fifteen infants and children with dilated cardiomyopathy underwent transvascular endomyocardial biopsy. The light and electron microscopic findings were reviewed to evaluate the presence of lymphocytes as an indicator of active myocarditis. Both ventricles were biopsied in 13 patients, and the right ventricle only was biopsied in 2. None of the endomyocardial specimens obtained by biopsy revealed an inflammatory process. Interstitial fibrosis, myofiber hypertrophy, degeneration and necrosis were found. Ultrastructural abnormalities of the mitochrondria, T tubules or Z bands were noted in approximately one-third of patients. Persistent, active myocarditis is an uncommon cause of dilated cardiomyopathy in children. Immunosuppressive therapy, which may be harmful, should be considered only after myocardial inflammation has been documented by endomyocardial biopsy.

(Am J Cardiol 1985;55:143–145)

Dilated cardiomyopathy (DC) remains a therapeutic challenge because it lacks specific etiologic factors. Goodwin[1] suggested that an antecedent viral infection may trigger a chronic inflammatory reaction of the myocardium in some patients. Recent studies in adults with idiopathic DC have reported inflammation in 5 to 63% of patients studied by transvascular endomyocardial biopsy techniques.[2–5] Clinical and hemodynamic improvement was noted in 10 of the 17 reported patients treated with immunosuppressive agents after biopsy confirmation of myocardial inflammation.[2,3] However, these observations were made in noncontrolled clinical trials in adults. The present report presents our experience in 15 infants and children with DC who underwent endomyocardial biopsy.

Methods

Patients: Since 1975, 32 patients with cardiomyopathies have undergone transvascular endomyocardial biopsy at the Childrens Hospital of Los Angeles. Fifteen infants and children had DC and constitute the study group of this report. The other 17 patients had hypertrophic or restrictive cardiomyopathy and were excluded from further analysis. The 15 study patients had chronic congestive heart failure that could not be attributed to a structural cardiac malformation. Echocardiography was performed before biopsy in all patients, using standard techniques.

Endomyocardial biopsy: All patients underwent routine diagnostic left- and right-sided cardiac catheterization and biplane cineangiography before endomyocardial biopsy. Emphasis was placed on the angiographic demonstration of normal coronary arteries. Transvascular endomyocardial biopsy was then performed as previously described.[6,7] Right and left ventricular (RV and LV) biopsies were attempted in all patients. Each biopsy sample obtained was approximately 1.5 × 1 × 1 mm or less and was placed into 2% buffered glutaraldehyde for light microscopy and transmission electron microscopy. Both light and electron microscopic sections were examined for evidence of inflammation.

Results

The clinical and echocardiographic features of the 15 patients with DC are summarized in Table I. The mean age (± standard error of the mean) at the time of biopsy was 4.6 ± 1.4 years (range 1 month to 15 years). The mean duration of illness was 0.9 ± 0.3 years (range 1 month to 5 years). In 9 patients, cardiac biopsy was performed within 6 months and in 4 patients within 2 months of the onset of congestive heart failure.

The LV end-diastolic dimensions in DC patients were uniformly increased and averaged 166% of the mean for normal subjects.[8] The LV shortening fraction was depressed in all patients (mean 13 ± 2%) and the ratio of

From the Division of Cardiology, Department of Pediatrics, and the Department of Pathology, Childrens Hospital of Los Angeles and the University of Southern California School of Medicine, Los Angeles, California. Manuscript received July 6, 1984; revised manuscript received August 27, 1984, accepted August 29, 1984.

Address for reprints: Alan B. Lewis, MD, Division of Cardiology, Childrens Hospital of Los Angeles, 4650 Sunset Boulevard, Los Angeles, California 90027.

TABLE I Clinical Profile of Patients with Dilated Cardiomyopathy

Pt	Age at Biopsy	Sex	Duration of Illness	LV Dd (cm)	LV SF (%)	LV PEP/ET	Died (Age at Death)
1	1.7 yr	F	1.7 yr	3.4	9	0.69	+ (2.2 yr)
2	14 yr	M	6 wk	7.5	12	0.53	0
3	1.2 yr	M	8 mo	4.9	12	0.60	0
4	12 yr	F	6 mo	6.7	11	1.0	0
5	4 mo	M	1 mo	3.5	26	0.57	0
6	10 mo	F	4 mo	3.9	19	0.54	0
7	1 mo	M	1 mo	4.1	15	0.70	+ (1 yr)
8	8.8 yr	F	6 mo	5.2	6	0.66	+ (8.9 yr)
9	5.9 yr	M	5 mo	5.4	15	0.45	0
10	5.3 yr	M	5 yr	4.5	12	...	+ (8.5 yr)
11	11 mo	M	4 mo	4.2	12	...	0
12	2.4 yr	F	2 yr	5.0	5	0.55	+ (2.5 yr)
13	4 mo	M	1 mo	4.0	9	0.24	+ (1.5 yr)
14	15.3 yr	M	1 yr	7.3	23	...	+ (15.4 yr)
15	7 mo	M	7 mo	4.2	10	0.44	0

Dd = end-diastolic dimension; LV = left ventricular; PEP/ET = ratio of preejection period to ejection time; SF = shortening fraction; + = yes; 0 = no.

LV preejection period to ejection time was prolonged in 14 patients (mean 0.58 ± 0.05).

Antibody titers against echo, Coxsackie, EBV and adenoviruses had been obtained at the time of initial presentation in 11 patients and were considered negative (titer ≤1:8) in all but 1 child, who once had a titer against Coxsackie B_2 of 1:32. Serum carnitine levels were measured in 2 patients and were normal in both. Two patients had a family history of cardiomyopathy. In 1 family all affected persons were male (patient 13).[9]

RV and LV biopsies were performed successfully in 13 patients; in 2 patients, only RV specimens could be obtained. A total of 76 endomyocardial biopsy specimens were obtained. No evidence of an inflammatory cell process was found in any patient. Interstitial fibrosis (7 patients), myofiber degeneration (7 patients) or hypertrophy (6 patients) were the most frequently observed abnormalities. Ultrastructural changes in the mitochondria (3 patients), T tubules (4 patients) and Z-band configuration (3 patients) were noted less frequently.

Discussion

Recent reports have described lymphocytic myocardial infiltration in 5 to 63% of adult patients with previously unexplained DC.[2–5] These observations have provided impetus for the use of antiinflammatory agents such as prednisone and azathioprine for therapy. Indeed, these early reports suggest at least short-term improvement or stabilization in some patients with biopsy-proved inflammatory cardiomyopathy after treatment. However, none of these studies were controlled and the use of such therapy remains controversial.

Several investigators have proposed a viral etiology for persistent myocarditis.[1,10–12] However, documentation of an antecedent viral infection is uncommon in most patients with unexplained DC.[2] In persons with active viral myocarditis, antiinflammatory agents may be hazardous; animal studies suggest that immunosuppression may exacerbate viral myocarditis by inhibiting interferon synthesis.[13,14]

Zee-Cheng et al[3] postulated that the presence of T lymphocytes in the myocardium supports the concept that myocardial damage may be mediated by the immune system. Nevertheless, whether the inflammatory cell response is actually destructive, reparative or merely reactive to a more primary myocardial degenerative process is not known.[15] Two recent studies showed that the symptomatic improvement in some patients treated with corticosteroids did not correlate with the presence or absence of inflammatory cells in the myocardium.[16,17]

The chronic use of immunosuppressive agents such as prednisone and azathioprine in children carries a considerable risk of adverse effects, including potentially life-threatening infection, growth retardation and bone marrow suppression. Therefore, the potential for improving cardiac function must be balanced carefully against the risks of immunosuppressive therapy.

The 15 children in this report represent a fairly typical group of young patients with unexplained DC. Despite the small size of this series, at least several patients might have been expected to show evidence of myocardial inflammation if the incidence of persistent active myocarditis were similar in adults and children.[2–5] We do not believe that inadequacy of biopsy material can explain the lack of inflammatory findings since an average of 5 specimens was obtained in each patient. This compares favorably with the recommendation by Edwards et al[15] of at least 4 samples per patient because of the possibility of focal inflammation. In fact, our technique may maximize the yield, because both ventricles were biopsied in 13 of our patients, whereas only the right ventricle was biopsied in the previously reported adult series.[2–5,15]

Alternatively, a longer duration between the onset of symptoms and performance of endomyocardial biopsy may decrease the incidence of inflammation observed in biopsy specimens. The mean duration of illness in our pediatric patients was 11 months (range 1 month to 5

years) and compares favorably with the mean symptom duration of 17 months (range 1 week to 6 years) in the adult patients reported by Zee-Cheng et al,[3] in whom 63% had at least low-grade inflammatory changes. Patients with the most extensive inflammatory changes usually had been symptomatic for shorter periods before biopsy (less than 4 months).[3] In contrast, 6 children in our series underwent endomyocardial biopsy within 4 months of becoming symptomatic, and no inflammation was observed.

O'Connell et al[18] suggested that myocardial scintigraphy with gallium-67 citrate is a useful noninvasive method of identifying patients with DC who may have inflammatory changes. However, the incidence of biopsy-proved myocarditis was only 36% in patients with a positive gallium-67 scan.[19] One of our patients underwent gallium-67 scanning and was found to have moderate myocardial uptake. However, no evidence of inflammation was noted on any of the 6 biopsy samples obtained within 1 month of scintigraphy. Gallium-67 localizes not only in areas of inflammation and abscess, but also in ischemic regions of the myocardium[20] and muscle undergoing physiologic hypertrophy.[18] Thus, the lack of specificity of gallium-67 scintigraphy limits its usefulness in the definitive diagnosis of myocardial inflammation. Nevertheless, it may be a useful screening agent to aid in the selection of patients for endomyocardial biopsy.[19]

A family history of cardiomyopathy was present in 2 of our patients, 1 of whom had an x-linked mode of inheritance[9]; therefore, hereditary basis for DC may be more common in children than in adults. Nevertheless, the apparently low incidence of myocardial inflammation in this small series of children with DC should not preclude the continued search in other young patients for this condition. However, because the use of immunosuppressive agents carries considerable risk, conclusive documentation of myocardial inflammation by endomyocardial biopsy should be a prerequisite to the initiation of antiinflammatory therapy.

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Arrhythmias in Ischemic and Nonischemic Dilated Cardiomyopathy: Prediction of Mortality by Ambulatory Electrocardiography

JOHN HOLMES, MD, SPENCER H. KUBO, MD, ROBERT J. CODY, MD, and PAUL KLIGFIELD, MD

To test the hypothesis that ventricular arrhythmias detected by ambulatory electrocardiography can stratify mortality risk in patients with ischemic and those with nonischemic dilated cardiomyopathy, clinical, hemodynamic and neurohumoral findings were evaluated in 31 patients. By Kaplan-Meier analysis, the total population had 51% survival at 12 months and 19% survival at 25 months. Subgroups based on peak complexity of ventricular arrhythmias included 9 patients with simple ventricular arrhythmias (peak Lown grades 1 to 3) and 22 patients with complex ventricular arrhythmias (peak Lown grades 4 or 5). Clinical variables and baseline catecholamine levels and renin-angiotensin system activity were similar in the simple and complex arrhythmia subgroups. Patients with simple and those with complex arrhythmias were comparable by all hemodynamic indexes except for a higher mean pulmonary capillary wedge pressure in the complex arrhythmia subgroup. Survival was strikingly related to arrhythmias: mortality was 11% (1 of 9) in the simple ventricular arrhythmia subgroup and 59% (13 of 22) in the complex ventricular arrhythmia subgroup ($p < 0.025$ by log-rank test). Twelve patients died suddenly and 2 patients died in circulatory failure, and the risk of death was not affected by the etiology of cardiomyopathy. The higher mortality among the patients with complex arrhythmia could not be explained by the presence of elevated filling pressures alone. Thus, ambulatory electrocardiography can stratify mortality risk among patients with severe ischemic and nonischemic dilated cardiomyopathy. These data are consistent with the hypothesis that complex ventricular arrhythmias represent an independent mortality risk factor in this population.

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Detection of arrhythmias by ambulatory electrocardiography is of value for the stratification of risk of sudden death in patients who survive myocardial infarction,[1,2] but the independent predictive value of arrhythmias in most other cardiac diseases remains unknown. Although survival in severe congestive heart failure due to dilated cardiomyopathy (DC) has been related to the etiology of DC[3] and to ventricular performance,[3–6] the prognostic value of coexistent arrhythmias on the natural history of this entity remains controversial.[7,8] This study was designed to test the hypothesis that arrhythmias detected by ambulatory electrocardiography can stratify mortality risk in severe DC and to examine whether etiology, hemodynamic profile and neurohumoral status influence the relation of arrhythmias to subsequent mortality.

From the Division of Cardiology, Department of Medicine, The New York Hospital–Cornell Medical Center, New York, New York. Manuscript received April 10, 1984 revised manuscript received August 23, 1984, accepted August 27, 1984.

Address for reprints: Paul Kligfield, MD, The New York Hospital–Cornell Medical Center, 525 East 68th Street, New York, New York 10021.

Methods

Thirty-one patients with severe congestive heart failure due to ischemic or nonischemic DC were enrolled in this study from 1981 to 1983. All patients had been referred for vasodilator therapy because of poor clinical response to digitalis and diuretic drugs. Twenty-five were men and 6 were women, aged 34 to 78 years (mean 56). The mean follow-up period was 14 months (range 2 to 25).

Patients presented with severe congestive heart failure and were separated into ischemic and nonischemic etiologic subgroups (Tables I and II). The diagnosis of ischemic DC was made when there was documented previous myocardial infarction or by demonstration of occlusive coronary disease at cardiac catheterization (Table I). Nonischemic DC was diagnosed in patients with no history of ischemia of presumed idiopathic, postinfectious, postpartum, valvular, or alcoholic origin (Table II). Eleven patients underwent catheterization

TABLE I Clinical, Hemodynamic and Neurohumoral Profile of Patients with Ischemic Dilated Cardiomyopathy

Pt	Follow-Up (mo)	Alive/ Dead	Anti-arrhythmic Drugs	Clinical History	NYHA Class	MAP (mm Hg)	PCWP (mm Hg)	SVR (dynes cm s^{-5})	CI (l/min/m^2)	Age (yr)	NE (pg/ml)	PRA (ng/ml/hr)
Simple VPC Subgroup												
1	25	A	N	MI(C)	3.0	108	26	2736	1.93	47	ND	0.3
2	20	A	N	MI	3.0	94	8	2022	1.92	73	ND	1.0
3	12	A	N	MI	2.0	84	7	904	2.75	46	169	2.0
4	3	D	N	MI(C)	4.0	76	37	3211	1.00	65	868	30.0
5	7	A	N	MI	3.0	81	4	1201	2.30	58	257	29.0
Complex VPC Subgroup												
6	23	D	N	MI	4.0	80	21	2032	1.29	66	ND	14.0
7	16	A	Y	MI(C)	2.0	64	23	1248	1.86	56	ND	4.1
8	11	A	N	MI	2.0	81	24	1835	1.73	70	249	0.8
9	12	D	N	MI(C)	2.5	102	25	2357	1.73	50	341	0.2
10	10	D	N	MI	4.0	72	26	1951	2.46	64	591	10.0
11	8	A	N	MI	3.5	72	13	2220	1.36	74	649	13.0
12	7	D	N	MI	3.0	85	22	950	3.12	78	545	5.6
13	4	D	Y	MI	4.0	88	25	2304	1.49	50	842	1.1
14	4	D	N	MI	3.0	95	21	1248	2.43	61	582	1.8
15	2	D	Y	MI(C)	3.0	88	16	2056	1.50	63	751	6.2
16	2	D	N	MI(C)	4.0	70	26	1672	1.30	63	1649	53.0

C = catheterization and coronary angiography; CI = cardiac index; MAP = mean arterial pressure; MI = history of myocardial infarction; NA = not available; ND = not done; NE = norepinephrine; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; PRA = plasma renin activity; SVR = systemic vascular resistance; VPC = ventricular premature contraction.

TABLE II Clinical, Hemodynamic and Neurohumoral Profile of Patients with Nonischemic Dilated Cardiomyopathy

Pt	Follow-Up (mo)	Alive/ Dead	Anti-arrhythmic Drugs	Clinical History	NYHA Class	MAP (mm Hg)	PCWP (mm Hg)	SVR (dynes cm s^{-5})	CI (l/min/m^2)	Age (yr)	NE (pg/ml)	PRA (ng/ml/hr)
Simple VPC Subgroup												
17	21	A	Y	IDIO(C)	4.0	94	11	1950	2.58	65	ND	0.6
18	14	A	Y	ETOH	3.0	83	NA	1645	2.00	54	ND	ND
19	12	A	N	P.INFECT.	2.0	82	4	1982	2.35	53	696	13.0
20	9	A	N	IDIO	3.5	84	15	2114	1.97	65	474	3.8
Complex VPC Subgroup												
21	21	D	N	IDIO(C)	3.0	82	18	2114	1.47	43	268	7.4
22	11	D	Y	IDIO	2.0	88	10	1040	3.00	46	271	13.0
23	12	D	Y	ETOH	4.0	77	22	1296	2.10	45	694	2.0
24	12	D	N	P.PARTUM	4.0	60	20	1469	1.89	36	295	12.0
25	12	A	N	P.INFECT	3.0	112	21	2348	1.67	34	375	0.1
26	11	D	N	IDIO(C)	3.0	96	34	1479	1.88	42	1222	15.0
27	10	A	N	MVR(C)	2.0	96	26	1422	2.23	66	768	1.9
28	6	A	N	IDIO	4.0	91	26	1982	1.94	62	726	6.3
29	6	A	Y	P.INFECT	2.5	78	13	1240	2.31	51	125	13.0
30	6	A	N	MVR(C)	3.5	68	20	1662	1.38	50	576	47.0
31	6	A	N	ETOH/IDIO	3.0	91	35	2026	1.49	38	812	53.0

ETOH = alcohol abuse; IDIO = idiopathic; MVR = mitral valve replacement; P.INFECT = postinfectious; P.PARTUM = postpartum; other abbreviations as in Table I.

with coronary angiography, which confirmed the clinical diagnosis before entry.

Right-sided cardiac catheterization was performed in all patients a mean of 17 days (range 1 to 120) before or after ambulatory electrocardiography. Tests were performed within 10 days of each other in 87% (27 of 31) of the patients. Baseline hemodynamic values were measured while patients were receiving only digoxin and diuretic drugs. Plasma norepinephrine levels and plasma renin activity were measured in 25 and 30 patients respectively. These were obtained at the time of catheterization, according to previously described methods.[9]

At the time of ambulatory electrocardiography, 94% of the patients (29 of 31) were receiving digitalis preparations, 39% (12 of 31) were receiving long-acting nitrates and 26% (8 of 31) were receiving afterload-reducing agents. Antiarrhythmic drugs were continued in 26% (8 of 31) of the study patients during the period of ambulatory electrocardiography and throughout the follow-up period. Serum potassium levels measured at the time of ambulatory electrocardiography were normal in all patients. Serum digoxin levels, available in 23 of 31 patients, were within normal limits in all patients but one, who had only simple arrhythmias. Digitalis and diuretic therapy was continued in 94% of the study patients (29 of 31) after initial evaluation, and all patients subsequently received vasodilator therapy (hydralazine, prazosin, captopril, enalapril or nifedipine). Antiarrhythmic drugs (procainamide and quinidine) were continued during the follow-up period according to the patients' prestudy regimen.

Twenty-four-hour ambulatory electrocardiograms utilized simultaneous precordial recordings of modified leads V_1 and V_5. All recordings were initially scanned by a special technician using computer-assisted analysis (Avionics Trendsetter).

TABLE III Hemodynamic and Neurohumoral Profiles of Patients Based on Ventricular Arrhythmia Profiles

	Simple VPCs	Complex VPCs	p Value
Age (yr)	58 ± 9	55 ± 13	NS
Sex (M/F)	5/4	20/2	NS
NYHA functional class	3.1 ± .7	3.1 ± .7	NS (W)
% on antiarrhythmic therapy	22% (2/9)	27% (6/22)	NS
Mean arterial pressure (mm Hg)	87 ± 10	83 ± 13	NS
Pulmonary capillary wedge pressure (mm Hg)	14 ± 12	22 ± 6	p <0.01
Cardiac index (liters/min/m^2)	2.09 ± .51	1.89 ± .52	NS
Systemic vascular resistance (dynes cm s^{-5})	1,939 ± 713	1,725 ± 442	NS
Norepinephrine level (pg/ml)	493 ± 293	617 ± 359	NS
Plasma renin activity (ng/ml/hour)	9.3 ± 11.6	13.4 ± 17.0	NS (W)

NS = not significant; NYHA = New York Heart Association; VPCs = ventricular premature complexes; W = Wilcoxon rank-sum test.

Arrhythmias were independently evaluated by 2 physicians. Supraventricular arrhythmia analysis included quantification of mean and peak atrial premature complexes (APCs) per 1,000 total beats, and tabulation of APC complex couplets, paroxysmal atrial tachycardia, atrial fibrillation, flutter and sustained atrial tachycardia. Ventricular arrhythmia analysis included quantification of mean and peak ventricular premature complexes (VPCs) per 1,000 total beats, and tabulation of ventricular arrhythmia complexity by the Lown classification system,[10] including grades 3 (multiform, single VPCs), 4A (VPC couplets), 4B (VPC salvos or ventricular tachycardia) and 5 (early-cycle VPCs). Partition of ventricular ectopic frequency (grades 1 and 2) was based on a mean VPC density of 10 or more per 1,000 beats.

All deaths during the follow-up period were from cardiac causes. Classification of the type of death was based on evaluation of the state of circulation immediately before death, as described by Hinkle et al.[11] Accordingly, sudden death was defined as an abrupt, fatal disorder of cardiac rhythm in a patient whose cardiac performance, until that moment, had been adequate to sustain peripheral circulation. Circulatory failure death was defined as progressively impaired cardiac mechanical performance, with some time elapsing before ultimate cessation of the pulse and respiration.

Survival estimates were calculated using the Kaplan-Meier life-table technique, and comparisons were made using the log-rank test with and without stratification.[12] The comparability of mean group characteristics was evaluated by an unpaired Student *t* test or by the Wilcoxon rank-sum test, as appropriate. Arrhythmia prevalence rates were examined by chi-square analysis with Yates' correction. Values are expressed as mean ± standard deviation.

Results

The overall mortality was 45% (14 of 31) during the follow-up period. The survival was 51% at 12 months and 19% at 25 months. Twelve patients died suddenly and 2 died in circulatory failure.

Arrhythmias in dilated cardiomyopathy: A mean VPC frequency of 10 or more per 1,000 beats occurred in 39% (12 of 31) of our patients, while multiform VPCs were found in 87% (27 of 31). Ventricular couplets were present in 65% (20 of 31), VPC salvos or ventricular tachycardia in 39% (12 of 31), and early-cycle forms in 6% (2 of 31).

According to peak ventricular arrhythmia grade, 71% (22 of 31) of all patients had complex ventricular arrhythmias (Lown grades 4 or 5), including 29% (9 of 31) with VPC couplets, 35% (11 of 31) with VPC salvos or ventricular tachycardia and 6% (2 of 31) with early-cycle forms as the most advanced arrhythmia grade. Brief or sustained supraventricular arrhythmias were seen in 58% (18 of 31) of the patients.

Arrhythmia subgroups and survival: The patients were grouped according to complexity of ventricular arrhythmias. Nine patients had peak Lown grades 1 to 3 arrhythmia (simple ventricular arrhythmia subgroup) and 22 patients had peak Lown grade 4 or 5 arrhythmia (complex ventricular arrhythmia subgroup). Striking mortality distinction was apparent with arrhythmia stratification (Fig. 1): mortality was 11% (1 of 9) in the simple ventricular arrhythmia subgroup and 59% (13 of 22) in the complex ventricular arrhythmia subgroup ($p < 0.025$ by log-rank test). Specifically, the mortality was 67% (6 of 9) in patients with VPC couplets as their peak ventricular arrhythmia grade, 55% (6 of 11) for patients with ventricular tachycardia and 50% (1 of 2) for those with early-cycle forms.

Because the inclusion of Lown class 5 as a complex ventricular arrhythmia may not be applicable in this population, our data were reanalyzed after reclassifying the 2 patients in Lown class 5 according to their next

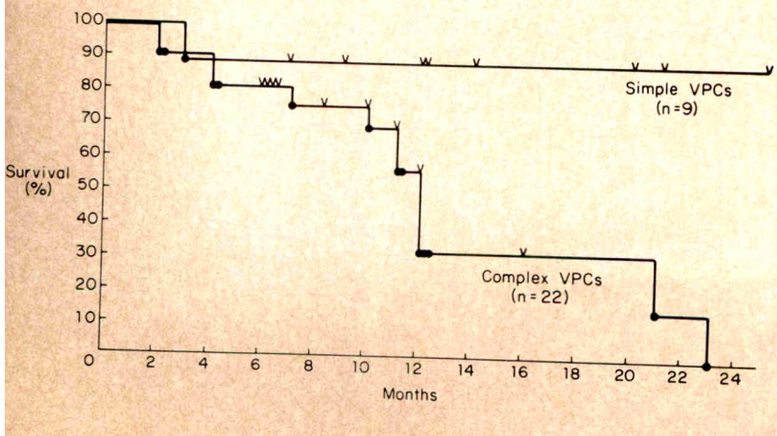

FIGURE 1. Kaplan-Meier survival curves in patients with dilated cardiomyopathy and peak Lown grade of 1 to 3 and 4A or higher. These curves are significantly different ($p < 0.025$) by the log-rank test. Survivors are denoted by **arrowheads** and nonsurvivors by **closed circles.** VPCs = ventricular premature complexes.

highest ventricular arrhythmia complexity grade. This had no effect on the significance of mortality differences between the simple and complex ventricular arrhythmia subgroups ($\chi^2 = 6.25$, $p < 0.025$).

Comparability of arrhythmia subgroups: Hemodynamic, clinical and neurohumoral summary profiles of subgroups based on arrhythmia complexity are shown in Table III. The only variable that was significantly different between the simple and complex arrhythmia patients was mean pulmonary capillary wedge pressure, which was 14 mm Hg in the simple ventricular arrhythmia subgroup and 22 mm Hg in the complex ventricular arrhythmia subgroup. However, analysis of survival distributions with respect to an elevated wedge pressure (defined as greater than 18 mm Hg) revealed no significantly excess mortality associated with high filling pressures ($\chi^2 = 1.44$, p = not significant [NS]). Further, comparing survival distributions of simple and complex ventricular arrhythmia subgroups when stratified for the presence of an elevated wedge pressure indicated a persistent trend toward a higher mortality in the complex arrhythmia subgroup ($\chi^2 = 2.03$, $0.10 < p < 0.15$).

The specific effects of wedge pressure and ventricular arrhythmias on mortality are shown in Table IV. Among patients with simple VPCs, the 1 patient who died had a pulmonary capillary wedge pressure greater than 18 mm Hg and a cardiac index of 1.00 liter/min/m^2, the lowest value of any patient in the study. However, in patients with complex ventricular ectopy, the mortality was the same in patients with high and those with low pressures (59% and 60%, respectively). Findings were also comparable when wedge pressure was partitioned at 16 mm Hg (61% vs 50%) or at 20 mm Hg (60% and 57%). Similarly, the higher mortality associated with complex ventricular arrhythmias remained significant when patients were stratified for age (partitioned at 60 years, $p < 0.05$) and cardiac index (partitioned at 2.0 liters/min/m^2, $p < 0.025$).

Arrhythmias in etiologic subgroups: Sixteen patients had ischemic DC and 15 had nonischemic DC. No

TABLE IV Dilated Cardiomyopathy: Effect of Ventricular Arrhythmias and Pulmonary Wedge Pressure on Mortality

	Ventricular Arrhythmias	
	Simple	Complex
PWP ≤18 mm Hg	0% (0/16)	60% (3/5)
PWP >18 mm Hg	33% (1/3)	59% (10/17)

PWP = pulmonary wedge pressure.

significant frequency or complexity differences between subgroups were found with respect to non–mutually exclusive categories of ventricular arrhythmias (Fig. 2) or peak Lown grade (Fig. 3). Sustained supraventricular arrhythmias (atrial fibrillation, flutter and sustained atrial tachycardia) occurred in 25% (4 of 16) of patients with ischemic DC and in 20% (3 of 15) of patients with ischemic DC (NS).

Etiologic subgroups and survival: Survival distributions were also drawn to examine the effect of etiology on mortality in DC subgroups with comparable arrhythmias. The 16 patients with ischemic DC and 15 with nonischemic DC were comparable by all hemodynamic, neurohumoral and historical variables except for age (Table V). Patients with ischemic DC were significantly older than those with nonischemic DC (62 vs 50 years, $p < 0.01$). The 1-year mortality was 44% in patients with nonischemic DC and 54% in patients with ischemic DC by Kaplan-Meier life-table analysis. Log-rank analysis of these survival distributions with stratification for increased age revealed no significant differences during the follow-up period ($\chi^2 = 0.42$, NS).

Comparison of survivors and nonsurvivors: Population profiles and hemodynamic and neurohumoral findings in the survivors and nonsurvivors were compared to determine if any characteristic other than ventricular arrhythmia complexity could identify patients most likely to die. No significant difference between survivors and nonsurvivors was found for age or

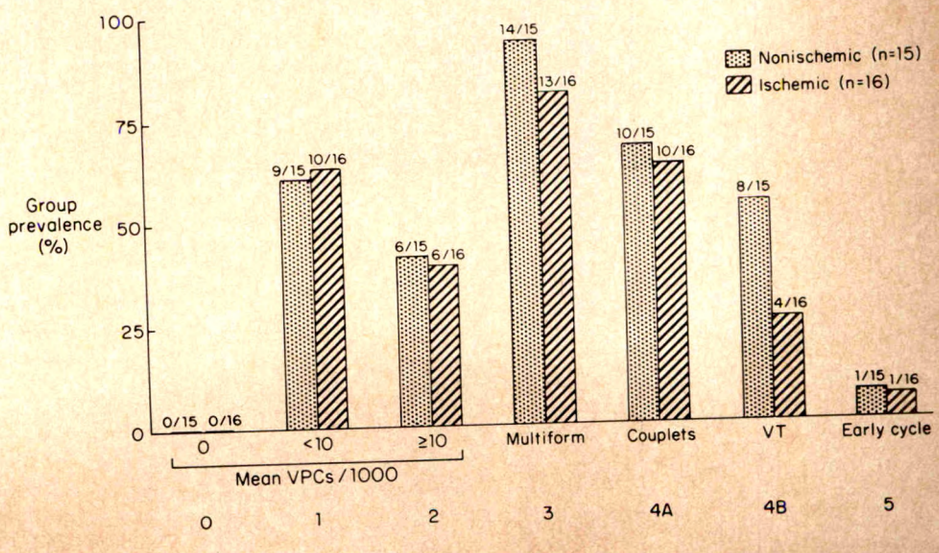

FIGURE 2. Ventricular arrhythmias in patients with ischemic and nonischemic dilated cardiomyopathy, expressed as the group prevalence of ventricular arrhythmia frequency and complexity characteristics. Each patient must appear once in the appropriate mean ventricular premature complex (VPC) density category. Each patient may also be represented in as many complexity categories as applicable, which include multiform ventricular premature complexes, couplets, ventricular tachycardia (VT) and early-cycle forms. The lower numbers refer to the Lown category corresponding to each frequency or complexity characteristic. Unlike the mutually exclusive hierarchy of the Lown scoring system, however, in this display all arrhythmias are represented according to their actual prevalence.

TABLE V Hemodynamic and Neurohumoral Profiles of Patients with Ischemic and Nonischemic Dilated Cardiomyopathy

	Ischemic	Nonischemic	p Value
Age (yr)	62 ± 10	50 ± 11	p <0.01
Sex (M/F)	13/3	12/3	NS
NYHA functional class	3.1 ± .7	3.1 ± .7	NS (W)
% on antiarrhythmic therapy	19% (3/16)	33% (5/15)	NS
Mean arterial pressure (mm Hg)	84 ± 12	86 ± 13	NS
Pulmonary capillary wedge pressure (mm Hg)	20 ± 9	20 ± 9	NS
Cardiac index (liters/min/m^2)	1.89 ± .56	2.02 ± .44	NS
Systemic vascular resistance (dynes cm s^{-5})	1,872 ± 644	1,697 ± 379	NS
Norepinephrine level (pg/ml)	624 ± 398	562 ± 300	NS
Plasma renin activity (ng/ml/hour)	10.7 ± 14.8	13.4 ± 16.4	NS (W)

NS = not significant; NYHA = New York Heart Association; W = Wilcoxon rank-sum test.

sex. Mean cardiac index (1.99 vs 1.90 liters/min/m^2), mean arterial pressure (86 vs 83 mm Hg), pulmonary capillary wedge pressure (17 vs 23 mm Hg) and systemic vascular resistance (1,796 vs 1,799) were not significantly different in survivors and nonsurvivors. There was also no significant difference in utilization of antiarrhythmic medications (24% vs 29%), mean functional class rating (2.9 vs 3.4), plasma renin activity (11.9 vs 12.2 ng/ml/hour) and plasma norepinephrine levels (500 vs 686 pg/ml) between survivors and nonsurvivors.

Discussion

Our data demonstrate that complex ventricular arrhythmias are strong predictors of cardiac death in patients with severe ischemic and nonischemic DC and suggest that the excess mortality risk conferred by complex ventricular arrhythmias is not totally dependent upon an association with poor ventricular function. These findings have important implications for risk stratification in heart failure intervention trials.

Our survival data agree with previous reports which have shown a high mortality in patients with DC.[3,4] A recent study of 182 patients with severe heart failure secondary to ischemic and nonischemic disease revealed a 66% 1-year survival,[3] which is similar to the 51% 1-year survival in our patients. Fuster et al[5] found similar results in 104 patients with idiopathic cardiomyopathy. In an earlier report by Hamby et al,[13] complex ventricular arrhythmias were frequently observed in patients with nonischemic cardiomyopathy, but prognosis was more closely related to the extent of failure than to arrhythmias.

Higher mortality in patients with congestive heart failure who have ventricular tachycardia were reported by Graboys et al[14] and Follansbee et al.[15] Meinertz et al[8] described an independent association between the frequency of VPC couplets and salvos and sudden death in patients with idiopathic DC. These findings are confirmed and extended by our study. In contrast, Huang et al[16] found no correlation between the presence of ventricular tachycardia and short-term prognosis in idiopathic cardiomyopathy. However, their 9% mortality during a mean follow-up period of 34 months is in sharp contrast to our 45% mortality during a mean follow-up period of 14 months. The low death rate found by Huang et al may have limited insights regarding predictors of mortality.

Wilson et al[7] reported that short-term survival in severe congestive heart failure was related to both functional status and the presence of 5 or more consecutive VPCs, but suggested that functional class was the only independent predictor of mortality. However, ventricular tachycardia and poor functional class were found significantly predictive of death only during the first 4 months of follow-up in that study. In contrast, we found no significant difference between the survival curves of patients in functional class IV compared with all other subjects. Moreover, when patients in functional

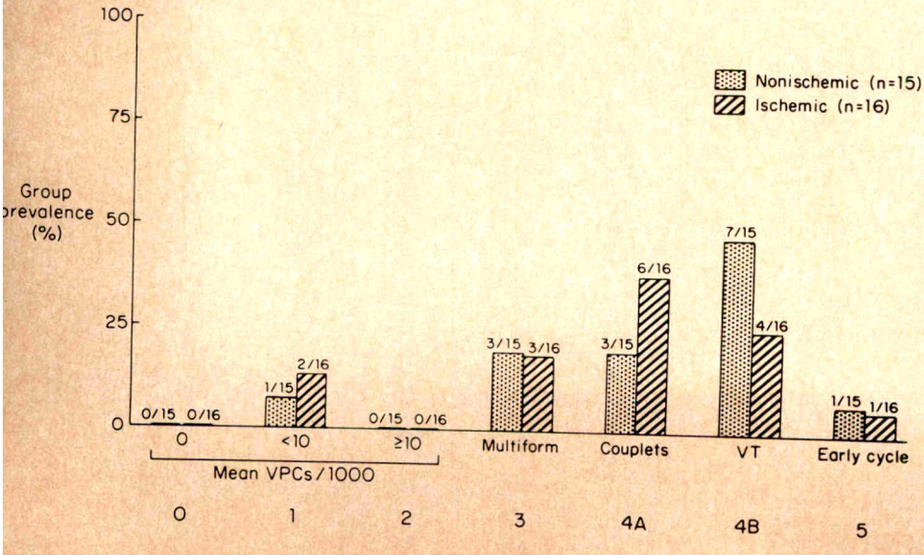

FIGURE 3. Peak grading of ventricular arrhythmias in patients with ischemic and nonischemic dilated cardiomyopathy. The ventricular arrhythmia frequency and complexity characteristics are as described in Figure 2. However, in this display each patient is represented only once, in the most advanced applicable Lown category. VPCs = ventricular premature complexes; VT = ventricular tachycardia.

class IV were eliminated from evaluation, the higher mortality associated with complex ventricular arrhythmias remained evident ($p < 0.025$). These contrasting findings might be explained by differences in patient selection and arrhythmia classification. Wilson et al evaluated patients with VPC couplets, triplets and 5-beat runs of ventricular tachycardia (but not early-cycle forms) as independent subgroups, rather than combining them as complex ventricular arrhythmias.

The 1-year mortality by Kaplan-Meier analysis for both patients with ischemic DC and those with nonischemic DC in our study was similar—54% and 44%, respectively. Our observation that prognosis is not markedly affected by etiology of DC confirms the experience of Wexler et al,[17] but is in contrast to data reported by Franciosa et al,[3] who found a 46% 1-year mortality among patients with ischemic DC but only a 23% mortality in patients with nonischemic DC. Although mortality differences between etiologic subgroups might be explained if cardiac function were different, their 2 groups of patients were reportedly comparable by historical and hemodynamic variables. However, ambulatory electrocardiograms were not evaluated in their population. In view of our data, differences in subgroup survival may thus reflect differences in ventricular arrhythmias in their subgroups rather than etiologic differences in natural history.

Potential limitations: Uncertainty regarding preterminal hemodynamic characteristics of patients and the nonuniformity of medical therapy after ambulatory electrocardiography are the major limitations of this study. However, vasodilator and antiarrhythmic drugs were maintained in a similar proportion of patients in the simple and complex ventricular arrhythmia populations, and further, antiarrhythmic drugs were not altered during the study. The impact of vasodilator therapy on ventricular arrhythmias in DC is unknown. Although such therapy could favorably influence hemodynamics and improve arrhythmias associated with poor ventricular function, excessive hypotension and the presence of digitalis and diuretic-induced metabolic derangements might adversely effect ventricular irritability. Despite these theoretical considerations, arrhythmias in our population did not appear to be markedly influenced by initial therapy. Supporting this is the observation that in 6 patients who underwent repeat 24-hour ambulatory electrocardiography after 1 week of vasodilator therapy, no patient changed peak Lown grade and no patient showed a significant change in mean or peak VPC frequency.

Clinical implications: These data are consistent with the hypothesis that complex ventricular arrhythmias represent an independent mortality risk factor in patients with severe DC. Further studies to identify the mechanisms of complex ventricular arrhythmias, as well as prospective antiarrhythmic trials, may be warranted in this population, particularly in a subset now identified as being at increased risk for death. However, our data should not be seen as a proposal that patients with DC undergo empiric antiarrhythmic therapy. It remains to be demonstrated that complex arrhythmias can be adequately suppressed by current therapeutics in patients with severely subnormal ventricular function. Further, the danger of potentially ineffective, or even harmful, therapy on an already compromised myocardium must be acknowledged.

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Value of Image Enhancement and Injection of Contrast Medium for Right Ventricular Volume Determination by Two-Dimensional Echocardiography in Congenital Heart Disease

PETER E. LANGE, MD, PETER A. SEIFFERT, MD, FRANK PRIES, MD, ARMIN WESSEL, MD, DIETRICH G. W. ONNASCH, PhD, HANS-J. HAHNE, Dipl Math, and PAUL H. HEINTZEN, MD

To determine factors that influence the accuracy of echocardiographically estimated right ventricular volume and to improve the echocardiographic input information by applying image enhancement techniques, quantitative contrast echocardiography (4-chamber view) and biplane angiocardiography were performed in 23 children during routine diagnostic cardiac catheterization. Volumes calculated on the basis of unprocessed and processed echocardiographic cross sections (area-length method and sphere model) underestimated angiocardiographic volumes significantly ($p < 0.01$), and more so in end-diastole (50.6%) than in end-systole (35.9%). Thus, ejection fraction was significantly ($p < 0.01$) underestimated; mean values were 0.48 ± 0.12 and 0.60 ± 0.08, respectively. The best comparison between echocardiography and angiocardiography at end-diastole was achieved with the sphere model using image enhancement techniques and injection of contrast media, where $y = 0.54x - 6.8$, $r = 0.97$, $sy.x = 7.3$. Correlations, however, in which unprocessed echocardiograms were used showed only slightly less good correlations. With the 6 image-enhancement techniques, a more homogeneous structure of the image and a more distinct outline of the internal surface was achieved. The statistical error improved only slightly. The echocardiographic 4-chamber view allows right ventricular volume determination with an acceptable accuracy. Its underestimation is related to inadequate visualization of trabeculations and mainly to the models used. Application of image enhancement techniques allows easier outlining of the internal cavity surface. The advantage gained by the combination of contrast injection and image enhancement techniques does not warrant the routine central injection of available contrast material.

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Information about the right ventricular (RV) functional state before and after corrective and palliative surgery for congenital heart diseases is important. Quantitative angiocardiography is regarded as the most accurate method for this acquiring such information, but it is an invasive technique. As a noninvasive method, 2-dimensional echocardiography (2-D echo) appears promising. However, quantitative studies yielded only fair results.[1–6] Exact determination of the accuracy of its echocardiographic volume by RV casts, the classic method for the assessment of angiocardiographic volume determination,[7–9] is impractical because available materials do not allow a sufficient echocardiographic visualization of an actual cross section.[1,4,10] Most studies therefore assess the accuracy by comparison with the biplane angiocardiographic method.[2–6] To determine factors that influence the accuracy of echocardiographically determined RV volume measurements and to improve the echographic input information by the application of digital image enhancement tech-

From the Department of Pediatric Cardiology and Bioengineering, Klinikum der Christian-Albrechts-Universität zu Kiel, Kiel, Federal Republic of Germany. This study was supported in part by Grants HE 769/7 from Deutsche Forschungsgemeinschaft, Bonn, Federal Republic of Germany. Manuscript received June 11, 1984; revised manuscript received August 21, 1984, accepted August 22, 1984.

Address for reprints: Peter E. Lange, MD, Klinikum der Christian-Albrechts-Universität zu Kiel, Abteilung Kinderkardiologie, Schwanenweg 20, D-2300 Kiel 1, Federal Republic of Germany.

niques, quantitative contrast echocardiography (4-chamber view) and biplane angiocardiography were performed in 23 patients during routine diagnostic cardiac catheterization.

Methods

Study patients: Diagnoses of the 23 patients studied included patent ductus arteriosus (n = 2), pre- and postoperative tetralogy of Fallot (n = 3), transposition of the great arteries (n = 2), aortic stenosis and regurgitation (n = 2), ventricular septal defect and pulmonary stenosis (n = 2), atrial septal defect (n = 6), coarctation of the aorta (n = 3), pulmonary stenosis (n = 2) and no congenital heart disease (n = 1). The study included 8 patients aged 1 to 5 years, 5 aged 5 to 10 years, 4 aged 10 to 15 years and 6 aged 15 to 20 years. Thus, the age range was 1 to 20 years (mean 9) and body surface area was 0.46 to 1.90 m^2 (mean 1.10).

Data acquisition: Conventional angiocardiography (Pandoros, Siemens) and contrast 2-D echo (Roche RT 400, 2.8 and 3.5 MHz) were performed with a 6Fr or 7Fr Berman catheter inserted into the femoral vein, using a modified percutaneous Seldinger technique. Diatrizoate meglumine (Urografin®, Schering), 1 ml/kg (electrocardiogram triggered in diastole), was injected at 10 to 25 ml/s (mean 17) (Contrac®, Siemens) into the right ventricle and 5 to 10 ml cold 5% glucose or normal saline solution by hand into the right ventricle, right atrium or superior vena cava, with the patient in the supine position. Biplane angiocardiographic RV projections, as well as the echocardiographic 4-chamber view were recorded at 50 frames/s on videotape (Grundig) together with the electrocardiogram and identification number. For calibration purposes, a steel sphere of known diameter was filmed at the location occupied by the right ventricle during angiocardiography. Suspended respiration to minimize movement artifacts was achieved only in older children.

Image enhancement: For digitization of the echocardiographic series, which was stored on videotape, a 256 × 256 pixel, 8-bit gray-level matrix was used. Electrocardiographic-gated end-diastolic and end-systolic background and contrast frames were transferred to a standard digital disc (DEC RP04, 80 Mbyte) linked to a minicomputer (DEC PDP 11/40). Details of the digital image processing equipment[11] and techniques for enhancement[18] have been described. Images were chosen for further processing only if they correlated well with respect to movement of thorax and diaphragm with all other images in the group to be averaged. Details of the averaging technique are shown in Figure 1.

With reference to the electrocardiogram, 2 images around end-diastole and end-systole of 4 subsequent background and 3 of 2 subsequent contrast cardiac cycles were selected. Thus, for both cardiac phases at each location of the image, 8 background and 6 contrast echo amplitudes per pixel could be extracted for further processing. Such a set of amplitude samples was used to derive a representative gray level for each pixel of the background frames calculating: (1) mean value (MB), (2) standard deviation of the sample (SB) by calculating the square root of the mean squared deviation from the mean, and (3) median value (MED) by sorting the N = 8 amplitudes in descending order and then selecting the value at position N/2.

For contrast frames, the mean (MC), and for the 8 background plus 6 contrast frames together, the standard deviation (SBC) were calculated. For the exclusive display of contrast medium mean values were substracted: (4) SM = MC − MB, and normalized for the standard deviations, (5) SMB = SM/SB, and (6) SMC = SM/SBC (Fig. 1).

Measurements: Biplane angiocardiographic projections and the echocardiographic cross sections were assessed in a similar manner. This technique has been described.[12,13] Displayed on a television monitor, the biplane projections (steel sphere and ventricles in sinus beats) and echocardiographic cross sections were traced with an x/y coder using a resistance foil and stored on the disc of a mini computer (DEC PDP 11/60). In addition to the RV outlines, anatomically defined internal landmarks (Fig. 2) were marked and stored the same way. For calibration of the echographic image, a built-in system of defined distances was used.

Angiocardiographic RV volumes were calculated with the biplane multiple-slices method, the model volumes being corrected with factors appropriate for spatial orientation and cardiac phase.[8,9] The spatial ventricular axes between the center of the pulmonary valve ring and the apex, as well as between tricuspid valve and apex, were calculated on the basis of the respective landmarks (Fig. 2, upper panel). The mean diameter (MDA) is defined as the diameter of the sphere with the angiocardiographic volume of the right ventricle, obtained with the area-length method.

The echocardiographic volumes were calculated in 3 ways:
(1) $V = (\pi/6)\ MDE^3$, where MDE is the diameter of the circle with the area (A) of the echographic cross-section (sphere volume). (2) $V = (3/8\pi)\ A^2/TR$, where TR is the distance between the tricuspid valve (T) and the trabeculated portion (R) (area-length volume) (Fig. 2, lower panel); (3) $V = \pi/6\ TR^3$.

The difference between end-diastolic and end-systolic volume is the stroke volume and the ratio stroke volume/end-diastolic volume, the ejection fraction. To characterize the shape TR was divided by MDE.

Results

Of 35 patients who underwent angiocardiography and echocardiography, 23 were included in this study. The reasons for exclusion were premature ventricular complexes during angiocardiography in 1 patient (precluding adequate opacification of the second post-extrasystolic beat), technical malfunction of the videotape in 4 patients and inadequate contrast of the echographic RV cross section in 7 patients. Results of the regression analysis of the relation between angiocardiographic volumes as reference and the different

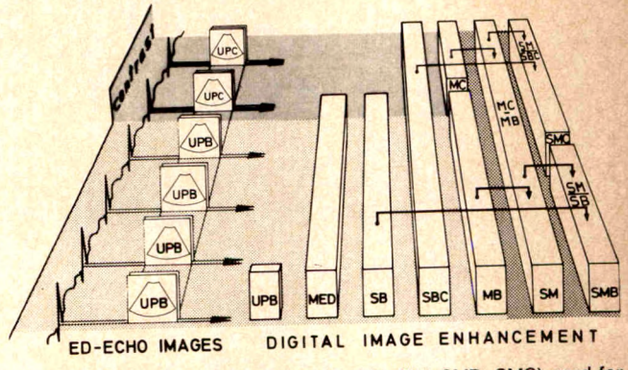
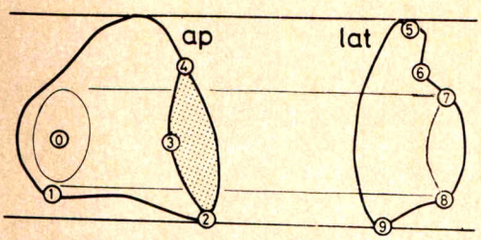


FIGURE 1. The 6 methods (MED, SB, MB, SM, SMB, SMC) used for digital enhancement of television images of 2-dimensional echocardiographic series. Contrast = images after the injection of cold normal saline solution and 5% glucose into the superior vena cava, right atrium and right ventricle; ED-ECHO = end-diastolic echocardiographic; MB = mean value of UPB; MC = mean value of UPC; MED = median value; SB = standard deviation of UPB; SBC = standard deviation of UPB plus UPC; SM = MC-MB; SMB = SM/SB; SMC = SM/SBC; UPB = unprocessed background; UPC = unprocessed contrast.

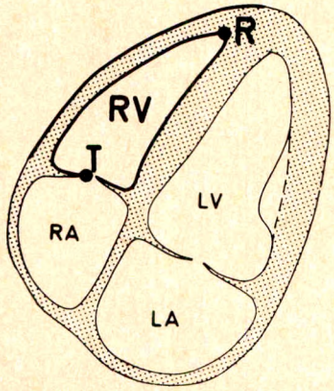
echocardiographic volumes are summarized for sphere volumes in Table I. Volumes calculated on the basis of processed as well as unprocessed echocardiographic cross-sections underestimated the angiocardiographic volumes significantly ($p < 0.01$) and significantly more ($p < 0.001$; paired t test) in end-diastole than in end-systole (Table I). Unprocessed echo underestimated the angio ejection fraction significantly ($p < 0.01$), the mean values being 0.480 ± 0.120 and 0.595 ± 0.077, respectively. The correlation was $r = 0.55$.

When angio- and echographic volumes were correlated (Table II), similar statistical errors were found for the echo volumes calculated with the sphere model as with the area-length formula, whereas the highest error was found for the volume calculated only on the basis of the long-axis TR (Fig. 2). With all image enhancement techniques, a more homogeneous structure of the image and a more distinct outline of the internal surface of the cavity was achieved (Fig. 3). When echographic and angiographic volumes were compared (Table I, Fig. 4), the lowest statistical errors were observed using the median value ($r = 0.970$) and contrast echo after normalized background subtraction using SMB ($r = 0.974$).

The shape of the echocardiographic cross section (4-chamber view, unprocessed background), expressed as the ratio TR/MDE, was slightly more circular in end-systole than in end-diastole, but this difference did not reach statistical significance (Table III). In contrast, the spatial angiocardiographic shape expressed as ratio axis pulmonary valve–apex/MDA and axis tricuspid valve–apex/MDA was significantly less spherical ($p < 0.01$) in end-systole (Table III).



ANGIOCARDIOGRAPHIC PROJECTIONS



ECHOCARDIOGRAPHIC 4-CHAMBER VIEW

FIGURE 2. Angiocardiographic and echocardiographic input information. Numbers of the angiocardiographic projections and letters of the 4-chamber view refer to anatomic landmarks stored in the computer for further processing. ap = anterior-posterior; LA = left atrium; lat = lateral; LV = left ventricle; T = tricuspid valve; R = apex of trabeculated portion; RA = right atrium; RV = right ventricle.

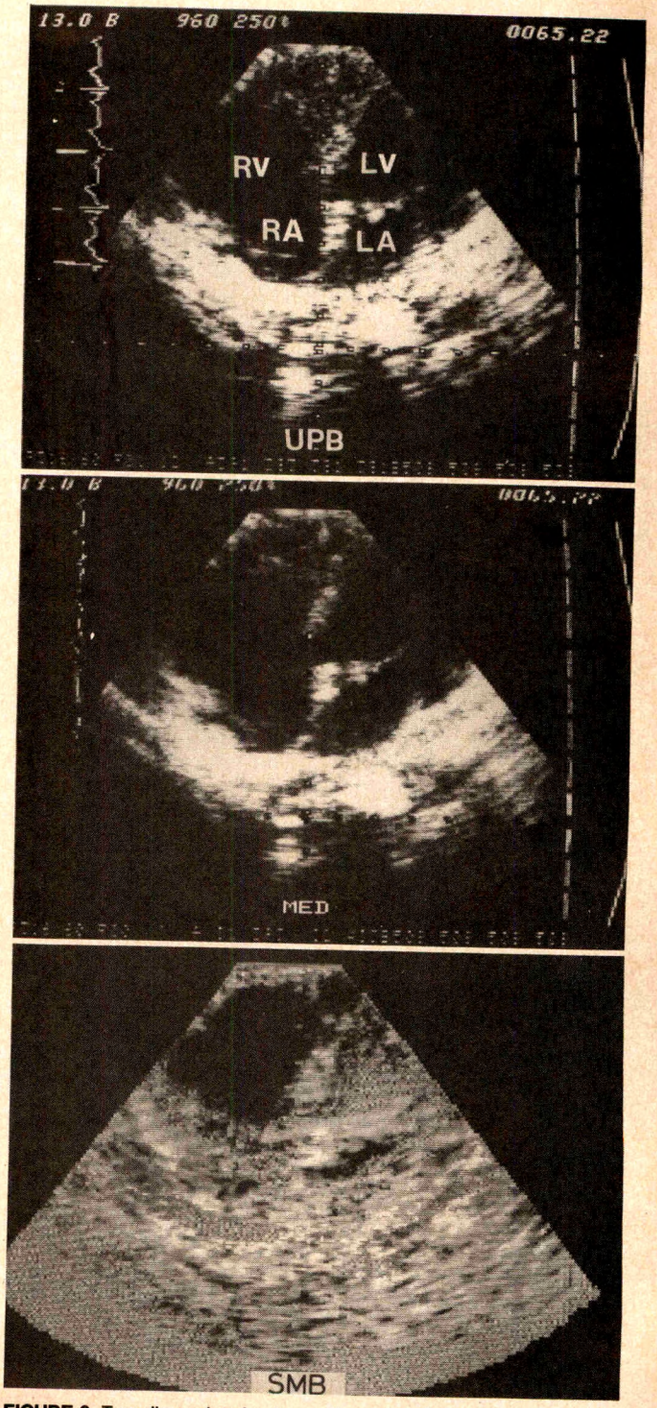


FIGURE 3. Two-dimensional-echocardiographic 4-chamber views. **Top,** unprocessed background (UPB); **middle,** processed background, median value (MED); **bottom,** contrast subtraction image (SMB) after injection of cold normal saline solution into the right ventricle. Image enhancement techniques achieve more homogeneous images (**middle and bottom**). Abbreviations as in Figure 2.

Based on angiographically determined spatial anatomic landmarks, the apex moved during systole 5.5 ± 2.8 mm superior, 1.6 ± 4.6 mm to the left and 1 ± 1 mm dorsal, while the center of the pulmonary valve ring moved 8 ± 5 mm inferior, 6.3 ± 4.7 mm to the left and 6.8 ± 5.1 mm anterior. Thus, the ventricular axis pulmonary valve ring/apex tilted 4.3 ± 2.2° during systole.

Discussion

Systematic error: Our results indicate that 2-D echo underestimates angiocardiographic volumes signifi-

TABLE I Regression Analysis y = a + bx of Right Ventricular Volume Parameters (n = 23) Determined by Angiocardiography (x) and Echocardiography (y) Before and After Application of Different Image Enhancement Methods

	a (ml)	b	r	sy.x (ml)
		ANGIO—ECHO (UPB)		
EDV	−7.2	0.64	0.97	9.7
ESV	−0.3	0.71	0.95	6.5
SV	−5.1	0.56	0.92	8.0
EF	Diff.	−0.11	±0.10	p <0.001
		ANGIO—ECHO (MB)		
EDV	−6.9	0.61	0.97	9.2
ESV	0.3	0.65	0.95	5.5
SV	−5.5	0.54	0.92	7.7
EF	Diff.	−0.12	±0.10	p <0.001
		ANGIO—ECHO (SB)		
EDV	−5.5	0.57	0.97	8.4
ESV	1.2	0.56	0.96	4.5
SV	−4.3	0.53	0.93	7.0
EF	Diff	−0.09	±0.09	p <0.001
		ANGIO—ECHO (MED)		
EDV	−5.9	0.62	0.97	9.0
ESV	1.3	0.66	0.96	5.2
SV	−5.3	0.56	0.93	7.4
EF	Diff.	−0.13	±0.09	p <0.001
		ANGIO—ECHO (SM)		
EDV	−5.9	0.57	0.93	12.1
ESV	0.5	0.62	0.94	5.9
SV	−6.2	0.53	0.87	10.0
EF	Diff.	−0.13	±0.14	p <0.001
		ANGIO—ECHO (SMB)		
EDV	−6.8	0.54	0.97	7.3
ESV	0.4	0.58	0.95	5.3
SV	−6.8	0.51	0.93	6.7
EF	Diff.	−0.12	±0.10	p <0.001
		ANGIO—ECHO (SMC)		
EDV	−4.7	0.54	0.97	8.0
ESV	0.8	0.61	0.96	5.0
SV	−5.4	0.50	0.94	6.4
EF	Diff.	−0.13	±0.11	p <0.001

All echocardiographic volumes were determined using the sphere model.

ANGIO = angiocardiography; Diff. = pair difference ± standard deviation; ECHO = echocardiography; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; MB = mean value of unprocessed background; MED = median value; r = correlation coefficient; SB = standard deviation of unprocessed background; SM = mean value of unprocessed contrast − unprocessed background; SMB = SM/SB; SMC = SM/SBC; SV = stroke volume; sy.x = standard error of the estimate; UPB = unprocessed background.

TABLE II Unprocessed Echographic Versus Angiographic Volumes for 3 Echographic Models

	End-Diastole		End-Systole	
Model	r	v	r	v
Sphere	0.97	18%	0.95	24%
Area-length	0.95	24%	0.95	22%
TR^3	0.91	31%	0.79	53%

r = correlation coefficient; TR = echocardiographic long axis (Fig. 2); v = variation coefficient.

TABLE III Right Ventricular Shape Parameters (n = 23)

	Angio PA/MDA	Angio TA/MDA	Echo TR/MDE
ED	1.36 ± 0.11	1.13 ± 0.12	1.32 ± 0.15
ES	1.45 ± 0.11	1.19 ± 0.15	1.26 ± 0.13
ED-ES	−0.08 ± 0.10	−0.07 ± 0.11	0.06 ± 0.16
p Value	<0.001	<0.01	NS

ED-ES = systolic change, tested for being 0; MDA = mean diameter equal to the diameter of the sphere with the angiographic area-length volume; MDE = mean diameter equal to the diameter of the circle with echographic area; NS = not significant; PA = spatial distance pulmonary valve–apex; TA = spatial distance tricuspid valve apex; TR = distance tricuspid valve–apex in the echocardiographic cross section, as derived from landmarks (Fig. 2); other abbreviations as in Table I.

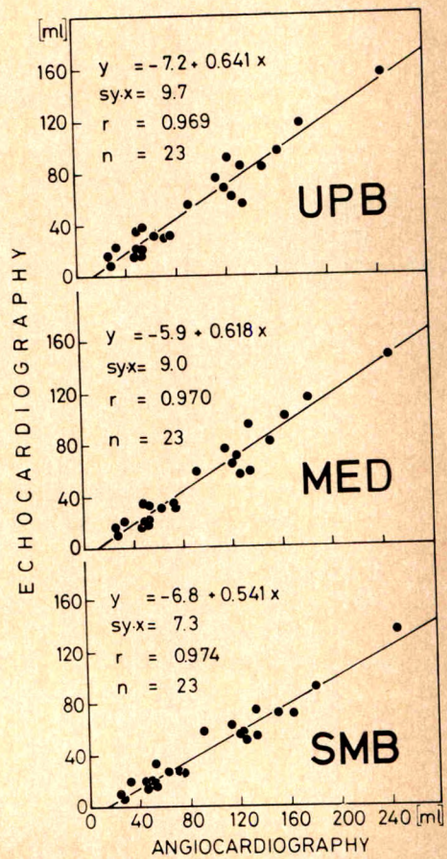


FIGURE 4. Relation between end-diastolic volumes, determined by angiocardiography and by echocardiography, using the sphere model. Application of image enhancement techniques (**middle**), as well as the additional injection of contrast media (**bottom**), achieve a more homogeneous image, allowing easier border recognition. The accuracy is, however, only minimally improved in comparison with the original image (**top**). sy.x = standard error of the estimate; other abbreviations as in Figure 1.

cantly (Table I, Fig. 4). The mean reason appears to be the limited echocardiographic input information. Calculation based on the typical triangular shaped cross section of inflow tract and trabeculated portion underestimates total RV volume if a sphere model is used (Table I, Fig. 4). Adjusting the model—a mathematical maneuver to prevent under- or overestimation—does not improve the accuracy of the method.[2,10] The input information remains unchanged. It appears to be easier and also appropriate to use a simple model like a sphere or ellipsoid and then correct the regression line to become the line of identity.

Another reason for the echocardiographic underestimation of angiocardiographic volumes is that roentgen contrast media surround the trabeculae carnea, thus including them within the angiographic outline, whereas the echocardiographic outline represents, in many instances, the innermost portions of the trabeculations, owing to the finite resolution of the echocardiographic beam. The resolution is limited laterally as well as perpendicularly to the scanning plane,[13–15] resulting in a left ventricular cavity outline that is inside the angiocardiographic border. Its visual limitations are especially obvious in the trabeculated portion of the right ventricle (Fig. 3). Only a very small part is included within the echocardiographic outline of the cavity.

Echocardiographic underestimation of the angiocardiographic volume was significantly less ($p < 0.01$) in end-systole than in end-diastole, the mean ratio echographic/angiographic volumes being 28% higher in end-systole. With the exception of the report of Silverman and Hudson,[5] such a difference has not been reported.[2,3,6] This result may be related in part to the different factors used for correction of the angiocardiographic model volumes. We are the only investigators who have used different factors for end-diastole and end-systole, the latter being approximately 15% smaller than the former.[8] In addition, the poorly visualized trabeculated portion should comprise a relatively larger area of the cross section in systole than in diastole compared with respective angiographic projections. Assessing the shape of the echocardiographic cross section, the end-diastolic/end-systolic echocardiographic information would appear to differ from angiocardiographic data. In contrast to the echocardiographic shape parameter, the angiographic parameters indicate a less spherical shape in end-systole (Table III). Little of the trabeculated portion and more of the inflow tract is visualized echographically, thus preventing quantitation of its changes during the cardiac cycle. An additional factor could be the superior systolic movement of the apex by 5° with respect to the pulmonary and tricuspid valves as well as with respect to the echocardiographic transducer. This different visualization of the right ventricle in diastole and systole is also responsible for the significant ($p < 0.001$) echographic underestimation of the angiographic ejection fraction (Table I).

The nonsimultaneous recording of angiocardiogram and echocardiogram could result in a larger angiographic volume, because flow and, presumably, RV volumes increase after injection of angiographic contrast medium into the right ventricle. Flow remains elevated at least 20 minutes after the injection of diatrizoate (Urografin).[16] This is when the echocardiographic recording was performed in all our patients.

Statistical error: The statistical errors relating echographic and angiographic volumes (Fig. 4, Table I) compare favorably with those previously reported[2–6]; they are at least as low as those found for the left ventricle.[14,17] This is surprising because the input information of the complex internal geometry obtained with the 4-chamber view is small (Fig. 3). The low statistical error (Table I, Fig. 4) indicates that the shape of the right ventricle is rather constant and that the 4-chamber view is comparably well reproducible, correcting for the different spatial orientations of the right ventricle in patients with different congenital heart diseases, a variety of which are included in this study. Attempts to increase the input information by using biplane echographic views and thus improve accuracy failed.[3,5,6,9] Standardization of these views appears to be too difficult. The gained information cannot compete with that of standard biplane angiocardiographic projections of the right ventricle. Also, reducing the input information to a single "standard dimension," as has been proposed by Bommer et al[1] on the basis of cast studies, may not be appropriate. When the area of the cross section was used to calculate RV volumes, significantly lower statistical errors resulted (Tables I and II) than if only 1 diameter (the long-axis TR) was used (Fig. 2, Table II). This finding suggests that such a standard dimension of the 4-chamber view varies more than the cross-sectional area.

Background images: The "noisy" appearance and the often poor border definition of the RV endocardial surface are limitations typical for 2-D echo images. To improve these limitations, different image enhancement techniques were applied. With use of all techniques, a homogeneous structure of the image and a more distinct outline of the internal surface of the RV cavity could be achieved in most cases (Fig. 3). The location of this internal border, however, is different for the 3 methods. Correspondingly, the calculated volumes are different (Table I). If such enhancement techniques are used in order to make outlining the RV cavity easier and faster, the same statistical method should be applied. In terms of statistical error, the median value offers the highest correlation coefficient and the lowest scatter of data (Table I, Fig. 4).

Contrast echocardiography and digital subtraction: Contrast echo to outline the RV inner surface is only useful in conjunction with background subtraction techniques (Fig. 1). Our group[18,19] and other investigators[20] have demonstrated the feasibility of this technique. Tracing the outline becomes easier and faster than it is after the application of background enhancement techniques. The achieved decrease of the statistical error, however, was only slight (Table I). The main reason was probably the contrast agents used, which did not distribute homogeneously enough.

Contrast echocardiographic volumes probably were consistently lower than noncontrast echocardiographic volumes (Table I), because in many regions the contrast

agent does not reach the internal surface of trabeculae carnae. Standardized bubbles may improve or abolish these disadvantages.

Acknowledgment: We thank Roswitha Bestehev and Iśa Schulze Brexel for their continuous and invaluable assistance.

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CME TEST #19

Baseline Rest Electrocardiographic Abnormalities, Antihypertensive Treatment, and Mortality in the Multiple Risk Factor Intervention Trial*

The University of Alabama School of Medicine designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. Answers are to be marked on the instruction sheet on page A165.

1. In the Multiple Risk Factor Intervention Trial (MRFIT), coronary artery disease (CAD) and total death rates were not anticipated to be so:
   a) high in the special intervention (SI) group
   b) high in the usual care (UC) group
   c) considerably low in both groups
   d) considerably high in both groups

2. Exercise testing was performed in the MRFIT only at the:
   a) prescreening of the study
   b) third screening
   c) second screening
   d) first screening

3. Men who were taking medicine and had a diastolic blood pressure of 90 mm Hg were assigned to:
   a) reach a goal of 80 mm Hg
   b) reach a goal of 50 mm Hg
   c) reach a goal of 89 mm Hg
   d) reach a goal of 70 mm Hg

4. With SI patients, serum levels of potassium were determined and reported:
   a) every 4 months
   b) every other visit
   c) every third visit
   d) none of the above

5. CAD deaths were subclassified as documented myocardial infarction and:
   a) sudden death within 60 minutes, or between 1 and 24 hours of symptom onset, without documented myocardial infarction
   b) congestive heart failure due to CAD
   c) death associated with surgery for CAD
   d) all of the above

6. MRFIT was not designed to:
   a) estimate the effect of a multifactor intervention program on CAD mortality
   b) estimate effect of individual intervention
   c) compare SI groups with UC groups
   d) do all the above

7. As of February 28, 1982, among UC men there were:
   a) 88 CAD deaths with electrocardiographic (ECG) abnormalities
   b) 88 CAD deaths without ECG abnormalities
   c) 68 CAD deaths with ECG abnormalities
   d) 68 CAD deaths without ECG abnormalities

8. Thirty-nine percent of ECG abnormalities were:
   a) high R waves
   b) negative T waves
   c) conduction defects
   d) left-axis deviation

9. Among men who had an exercise electrocardiogram, the percent with abnormal electrocardiographic responses during or right after the exercise test, using computer criteria, was:
   a) 8.2%
   b) 18%
   c) 12.2%
   d) 26%

10. In hypertensive men in the SI group, the strength of the association between reduction in the serum cholesterol level and CAD mortality:
    a) was higher with presence of ECG abnormalities
    b) was higher with absence of ECG abnormalities
    c) did not differ significantly with or without ECG abnormalities
    d) does not correlate

***This article appears on page 1 of this issue.**

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Introducing TONOCARD®

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a new oral agent for the suppression of symptomatic ventricular arrhythmias

Like lidocaine.

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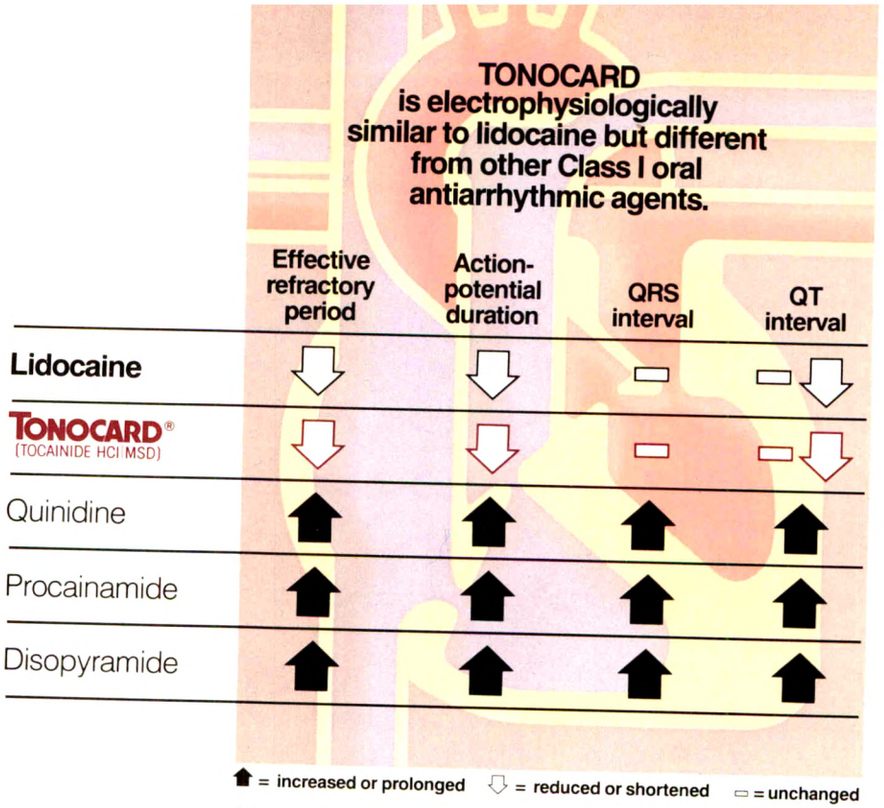


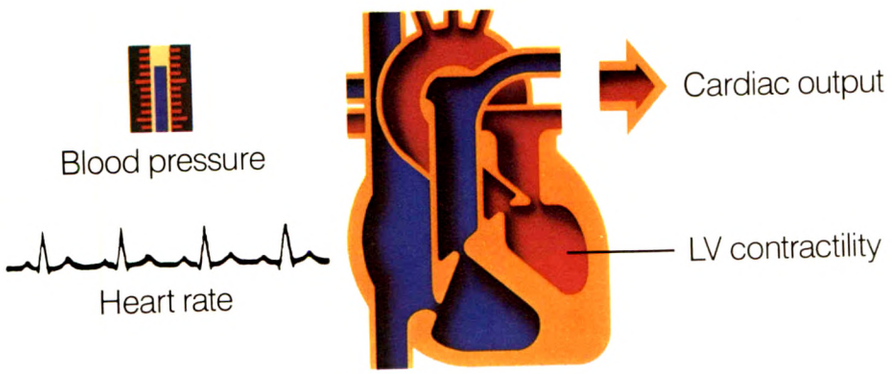
Adapted from Braunwald, E.: Pharmacologic treatment of cardiovascular disorders, in *Harrison's Principles of Internal Medicine*, ed. K. J. Isselbacher et al., 9th ed., New York, McGraw-Hill Book Company, 1980, pp. 1068-1069. Data derived from animal and human studies.

☐ Patients who respond to lidocaine also respond to TONOCARD in a majority of cases. Failure to respond to lidocaine usually predicts failure to respond to TONOCARD, but there are exceptions.

Therapeutically, it acts like lidocaine.

Clinical cardiac parameters were usually unchanged in well-compensated patients studied.

- In a long-term study of 72 post-myocardial infarction patients, TONOCARD (400 mg q 8 h) did not produce clinically significant changes in blood pressure, heart rate, or LV contractility.



- In catheterization studies, TONOCARD usually produced a small degree of depression in left ventricular function, but there were usually no changes in cardiac output or clinical evidence of increasing congestive heart failure.

TONOCARD has been used safely in patients with acute myocardial infarction and various degrees of congestive heart failure. It has, however, a small negative inotropic effect and can increase peripheral resistance slightly.

- TONOCARD should be used cautiously in patients with known heart failure or minimal cardiac reserve, particularly if a beta blocker is given as well, because of the potential for aggravating the degree of heart failure.

TONOCARD is contraindicated in patients who are hypersensitive to this product or to local anesthetics of the amide type and in patients with second- or third-degree atrioventricular block in the absence of an artificial ventricular pacemaker.

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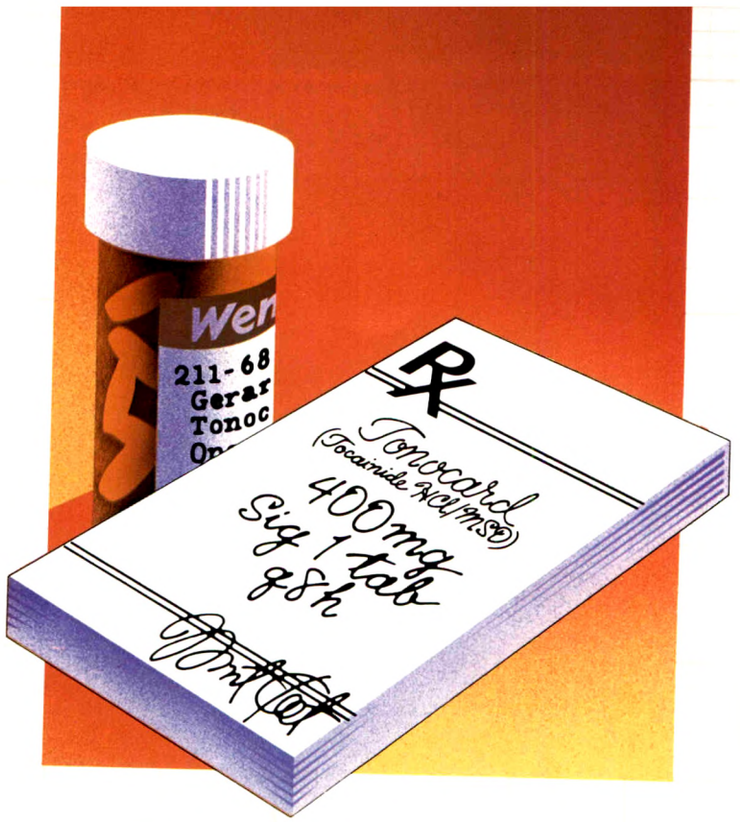

☐ Simple initial q 8 h dosage.

Unlike lidocaine, it's useful for maintenance therapy.

Recommended initial dosage is 400 mg every 8 hours; patients should then be carefully titrated on the basis of antiarrhythmic response and tolerance, both of which are dose-related. The usual adult dosage is between 1200 and 1800 mg/day, divided in three doses. Doses beyond 2400 mg have been administered infrequently. Patients who tolerate the t.i.d. regimen may be tried on a twice-daily regimen with careful monitoring. Some patients, particularly those with renal or hepatic impairment, may be treated with less than 1200 mg/day.

To help alleviate the most common adverse reactions, TONOCARD may be given with food (without affecting the extent of its bioavailability), the dosage reduced, or therapy discontinued.

Like other antiarrhythmics, tocainide has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like other antiarrhythmics, it has potentially serious adverse effects including the ability to worsen arrhythmias. It is therefore essential that each patient given tocainide be evaluated electrocardiographically and clinically prior to and during tocainide therapy to determine whether the response to tocainide supports continued treatment.

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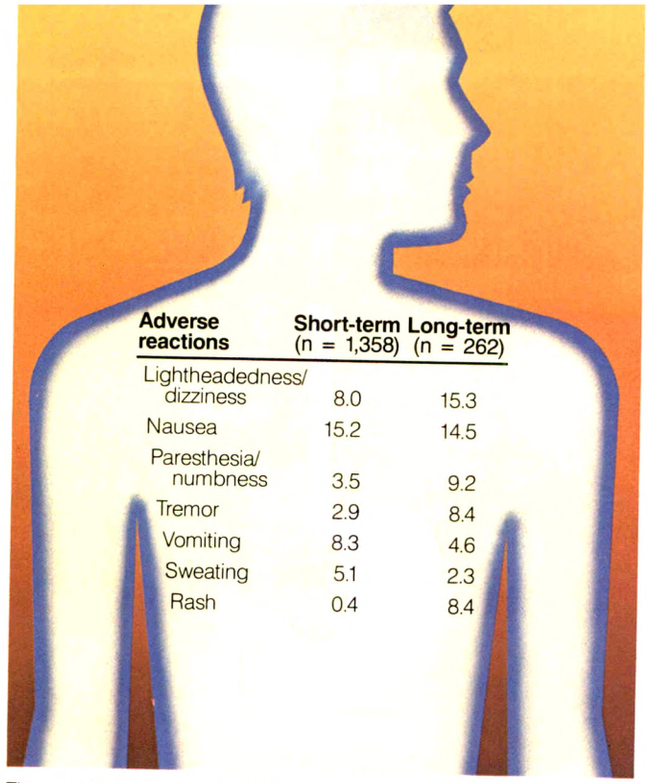


Reactions leading to therapy discontinuation occurred in 21% of patients in long-term (2 to 6 months) controlled trials.

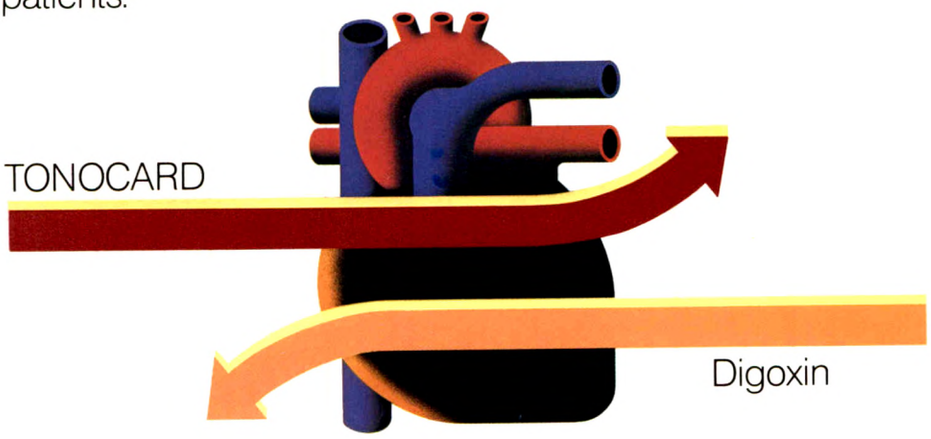
The most frequently reported adverse reactions, expressed as a percentage of patients receiving TONOCARD® (Tocainide HCl, MSD) in short-term and long-term controlled clinical trials.

- ☐ These adverse reactions were generally mild, transient, dose-related, and reversible with reduction in dosage, by taking the drug with food, or by therapy discontinuation.
- ☐ Tremor may be useful as a clinical indicator that the maximum dose is being approached.

CNS and GI reactions are common...

No interaction seen with digoxin.

- ☐ In specific interaction studies and open clinical studies with digoxin and TONOCARD, no clinically significant interaction was seen.
- ☐ TONOCARD is equally effective in digitalized and nondigitalized patients.



Other antiarrhythmics, anticoagulants, and diuretics were given with TONOCARD in open studies, without evidence of clinically significant interaction.

Beta blockers have been used with TONOCARD in open studies, without evidence of clinically significant interaction.

- ☐ However, in a specific interaction study, TONOCARD and metoprolol had additive effects on wedge pressure and cardiac index.

Caution should be exercised in the use of multiple-drug therapy.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing excessive depression of cardiac conductivity.

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but usually mild and manageable.

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An oral analog of lidocaine for the suppression of symptomatic ventricular arrhythmias

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Like other antiarrhythmics, tocainide has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given tocainide be evaluated electrocardiographically and clinically prior to, and during, tocainide therapy to determine whether the response to tocainide supports continued treatment.

CONTRAINDICATIONS: Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second or third degree atrioventricular block in the absence of an artificial ventricular pacemaker.

WARNINGS: ***Blood Dyscrasias:*** Leukopenia, agranulocytosis, hypoplastic anemia, and thrombocytopenia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill and who were receiving concomitant drugs. Patients should be instructed to promptly report the development of bruising or bleeding and any signs of infection such as fever, sore throat, or chills. Periodic blood counts are recommended, particularly during the first six months of therapy. If any of these hematologic disorders is identified, TONOCARD should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within one month of discontinuation (see ADVERSE REACTIONS).

Acceleration of Ventricular Rate: Acceleration of ventricular rate occurs infrequently when antiarrhythmics are administered to patients with atrial flutter or fibrillation (see ADVERSE REACTIONS).

PRECAUTIONS: *General:* ***Pulmonary Fibrosis:*** Pulmonary fibrosis, pneumonitis, alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, TONOCARD should be discontinued (see ADVERSE REACTIONS).

In patients with known heart failure or minimal cardiac reserve, TONOCARD should be used with caution because of the potential for aggravating the degree of heart failure.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing depression of cardiac conductivity.

In patients with severe liver or kidney disease, the rate of drug elimination may be significantly decreased (see DOSAGE AND ADMINISTRATION).

Since antiarrhythmic drugs may be ineffective in patients with hypokalemia, the possibility of a potassium deficit should be explored and, if present, the deficit should be corrected.

Like all other oral antiarrhythmics, TONOCARD has been reported to increase arrhythmias in some patients (see ADVERSE REACTIONS).

Drug Interactions: Specific interaction studies with digoxin and metoprolol have been conducted, no clinically significant interaction was seen with digoxin, but tocainide and metoprolol had additive effects on wedge pressure and cardiac index. TONOCARD has also been used in open studies with digitalis, beta-blocking agents, other antiarrhythmic agents, anticoagulants, and diuretics, without evidence of clinically significant interactions. Nevertheless, caution should be exercised in the use of multiple drug therapy.

TONOCARD is equally effective in digitalized and nondigitalized patients. In 17 patients with refractory ventricular arrhythmias on concomitant therapy, serum digoxin levels (11 ± 0.4 ng/mL) remained in the expected normal range (0.5-2.5 ng/mL) during tocainide administration.

Pregnancy: Pregnancy Category C: In a teratogenicity study in rabbits, tocainide was administered orally at doses of 25, 50, and 100 mg/kg/day (about 1 to 4 times the usual human dose). No evidence of a drug-related teratogenic effect was noted; however, these doses were maternotoxic and produced a dose-related increase in abortions and stillbirths. In a teratogenicity study in rats, an oral dose of 300 mg/kg/day (about 12 times the usual human dose) showed no evidence of treatment-related fetal malformations, but maternotoxicity and an increase in fetal resorptions were noted. An oral dose of 30 mg/kg/day (about twice the usual human dose) did not produce any adverse effects.

In reproduction studies in rats at maternotoxic oral doses of 200 and 300 mg/kg/day (about 8 and 12 times the usual human dose, respectively), dystocia, and delayed parturition occurred which was accompanied by an increase in stillbirths and decreased survival in offspring during the first week postpartum. Growth and viability of surviving offspring were not affected for the remainder of the lactation period.

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There are no adequate and well-controlled studies in pregnant women. TONOCARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether tocainide is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from TONOCARD, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: TONOCARD commonly produces minor, transient, nervous system and gastrointestinal adverse reactions, but is otherwise generally well tolerated. TONOCARD has been evaluated in both short-term (n = 1,358) and long-term (n = 262) controlled studies as well as a compassionate use program. Dosages were lower in most of the controlled studies (1200 mg/day) and higher in the compassionate use program (1800 mg and more). In long-term (2-6 months) controlled studies, the most frequent adverse reactions were lightheadedness/dizziness (15.3 percent), nausea (14.5 percent), paresthesia/numbness (9.2 percent), and tremor (8.4 percent). These reactions were generally mild, transient, dose-related and reversible with a reduction in dosage, by taking the drug with food, or by therapy discontinuation. Tremor, when present, may be useful as a clinical indicator that the maximum dose is being approached. Adverse reactions leading to therapy discontinuation occurred in 21 percent of patients in long-term controlled trials and were usually related to the nervous system or gastrointestinal system.

Adverse reactions occurring in greater than one percent of patients from the short-term and long-term controlled studies appear in the following table:

	Percent of Patients Controlled Studies	
	Short-term (n = 1,358)	Long-term (n = 262)
NERVOUS SYSTEM		
Lightheadedness/dizziness/vertigo/giddiness	8.0	15.3
Paresthesia/numbness	3.5	9.2
Tremor/quivering/tremulousness	2.9	8.4
Confusion/disorientation/hallucinations	2.1	2.7
Altered mood/awareness	1.5	3.4
Restlessness/shakiness/nervousness	1.5	0.4
Blurred vision/visual disturbances	1.3	1.5
Discoordination/unsteadiness/walking disturbances	1.2	0.0
Anxiety	1.1	1.5
Tinnitus/hearing loss	0.4	1.5
Ataxia	0.2	3.0
Nystagmus	0.0	1.1
GASTROINTESTINAL SYSTEM		
Nausea	15.2	14.5
Vomiting	8.3	4.6
Anorexia	1.2	1.9
Diarrhea/loose stools	0.0	3.8
CARDIOVASCULAR SYSTEM		
Hypotension	3.4	2.7
Bradycardia	1.8	0.4
Palpitations	1.8	0.4
Chest pain	1.6	0.4
Conduction disturbances	1.5	0.0
Left ventricular failure	1.4	0.0
OTHER		
Sweating/cold sweat/night sweats/clammy	5.1	2.3
Headache	2.1	4.6
Tiredness/drowsiness/fatigue/lethargy/lassitude/sleepiness	1.6	0.8
Hot/cold feelings	0.5	1.5
Rash/skin lesion	0.4	8.4

An additional group of about 2,000 patients has been treated in a program allowing for the use of TONOCARD under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy, and comparatively high doses of TONOCARD were used. Fifty-four percent of the patients continued in the program for one year or longer, and 12 percent were treated for longer than three years, with the longest duration of therapy being nine years. Adverse reactions leading to therapy discontinuation occurred in 12 percent of patients (usually central nervous system effects or rash). A tabulation of adverse reactions occurring in one percent or more of patients follows:

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	Percent of Patient Compassionate Us (n = 1,927)
NERVOUS SYSTEM	
Lightheadedness/dizziness/vertigo/giddiness	25.3
Tremor/quivering/tremulousness	21.6
Restlessness/shakiness/nervousness	11.5
Confusion/disorientation/hallucinations	11.2
Altered mood/awareness	11.0
Ataxia	10.8
Blurred vision/visual disturbances	10.0
Paresthesia/numbness	9.2
Nystagmus	1.1
GASTROINTESTINAL SYSTEM	
Nausea	24.6
Anorexia	11.3
Vomiting	9.0
Diarrhea/loose stools	6.8
CARDIOVASCULAR SYSTEM	
Increased ventricular arrhythmias/PVCs	10.9
CHF/progression of CHF	4.0
Tachycardia	3.2
Hypotension	1.8
Conduction disturbances	1.3
Bradycardia	1.0
OTHER	
Rash/skin lesion	12.2
Sweating/cold sweat/night sweats/clammy	8.3
Arthritis/arthralgia	4.7
Myalgia	1.7
Lupus	1.6

Adverse reactions occurring in less than one percent of patients in either the controlled studies or the compassionate use program are as follows:

Nervous System: Coma, convulsions/seizures, depression, psychosis, mental change, agitation, altered taste/smell, difficulty concentrating, diplopia, dysarthria, impaired memory, increased stuttering/slurred speech, insomnia/sleeping disturbance, local anesthesia, nightmares, thirst, weakness, myasthenia gravis.

Gastrointestinal System: Abdominal pain/discomfort, constipation, dysphagia, gastrointestinal symptoms (including dyspepsia).

Cardiovascular System: Ventricular fibrillation, extension of acute myocardial infarction, cardiogenic shock, angina, AV block, hypertension, increased QRS duration, pleurisy/pericarditis, prolonged QT interval, right bundle branch block, syncope, vaso-vagal episodes, cardiomegaly, sinus arrest.

Pulmonary System: Respiratory arrest, pulmonary edema, pulmonary embolism, pulmonary fibrosis, alveolitis, pneumonia, pneumonitis, dyspnea.

Other: Hematologic disorder (agranulocytosis, hypoplastic anemia, anemia, leukopenia, thrombocytopenia), increased ANA, urinary retention, polyuria/increased diuresis, alopecia, cinchonism, claudication, cold extremities, dry mouth, earache, edema, fever, hiccups, itching, leg cramps, malaise, metallic/menthol taste, muscle twitching/spasm, neck pain, pain radiating from neck, pallor/flushed face, pressure on shoulder, yawning.

Leukopenia, agranulocytosis, hypoplastic anemia, and thrombocytopenia, possibly drug related, have been reported (0.10 percent) in patients receiving TONOCARD in controlled trials and the compassionate use program. These hematologic disorders usually occurred after 2-12 weeks of therapy and two patients died. These events usually occurred in seriously ill patients who were receiving concomitant drugs known to be associated with hematologic disorders (see WARNINGS).

Pulmonary fibrosis, pneumonitis, alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. The incidence of pulmonary fibrosis was 0.03 percent in controlled trials and the compassionate use program. These events usually occurred in seriously ill patients. Symptoms of these pulmonary disorders and/or x-ray changes usually occurred following 3-18 weeks of therapy and two patients died (see PRECAUTIONS).

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Magnitude and Implications of Spontaneous Hemodynamic Variability in Primary Pulmonary Hypertension

STUART RICH, MD, GILBERT E. D'ALONZO, DO, DAVID R. DANTZKER, MD, and PAUL S. LEVY, ScD

The pulmonary artery (PA) pressure and pulmonary resistance at rest have been noted to vary spontaneously in patients with primary pulmonary hypertension. To evaluate this variation, in 12 patients (8 women, 4 men, aged 43 ± 13 years), hourly measurements were made for 6 consecutive hours of heart rate, systemic and PA pressures, cardiac output, systemic and pulmonary resistance. After these baseline measurements the patients were tested with hydralazine and nifedipine therapy. Spontaneous variability in pulmonary pressures and resistances occurred in each patient, with the amount of variation (coefficient of variation) in PA pressure averaging 8% and in total pulmonary resistance 13% over the 6 hours. The patients with the most variability in mean PA pressure also had the most variability in cardiac output ($r = 0.69$, $p = 0.02$). Variability also correlated with the severity of the disease, as the patients with the highest total pulmonary resistances also had the most variation for that factor ($r = 0.91$, $p < 0.01$). The amount of variability did not correlate, however, with the acute response to either hydralazine or nifedipine administration. Based on the average coefficients of variation in these 12 patients, estimates were obtained of the percent change needed for an observed change to be attributed to a drug effect with 95% confidence. From these estimates, it was projected that for a single patient, a mean change in pulmonary resistance of 36% or a mean change in PA pressure of 22% would be required in order to attribute the changes to a drug effect. Thus, spontaneous hemodynamic variability is a common phenomenon in patients with primary pulmonary hypertension and may account for substantial changes in PA pressure and pulmonary resistance at rest.

(Am J Cardiol 1985;55:159–163)

Vasodilator drugs have been reported to lower the pulmonary artery (PA) pressure and pulmonary vascular resistance in patients with primary pulmonary hypertension (PPH).[1–5] However, PA pressure and pulmonary resistance may change spontaneously, without any drug intervention.[6] The implications of this spontaneous variability are not clear, nor is it known if it is a common or unusual phenomenon. We monitored the pulmonary and systemic central hemodynamics of 12 patients with PPH every hour for 6 consecutive hours to determine their magnitude of variation. We then administered vasodilator drugs to these patients and noted if there was any relation between the magnitude of hemodynamic variability and drug responsiveness.

From the Department of Medicine, University of Illinois College of Medicine, Department of Medicine, University of Michigan Medical School, and the Epidemiology and Biometry Program, University of Illinois School of Public Health, Chicago, Illinois. Manuscript received June 21, 1984; revised manuscript received August 16, 1984, accepted August 20, 1984.

Address for reprints: Stuart Rich, MD, Section of Cardiology, University of Illinois Hospital, P.O. Box 6998, Chicago, Illinois 60680.

Methods

Subjects: The study includes 12 consecutive patients (8 women, 4 men) referred to the University of Illinois and University of Michigan Hospitals over a 1-year period for evaluation of PPH. They were aged 23 to 60 years old (mean 43 ± 13). Each underwent an extensive work-up to determine the cause of the pulmonary hypertension, but no cause was found.[7] Each patient was admitted to have hemodynamic testing for evaluation of vasodilator therapy while receiving no vasodilator drugs with the exception of digoxin and diuretic therapy.

Hemodynamic monitoring: A Swan-Ganz catheter was directed into the PA, and a small radial artery cannula was placed for hemodynamic monitoring. Each patient was monitored for at least 6 consecutive hours in an intensive care unit, and values were recorded every hour. Heart rate, systolic, diastolic and mean systemic and PA pressures, pulmonary wedge pressure, and right atrial pressure were recorded. Cardiac output was determined by the thermodilution tech-

TABLE I Hemodynamic Characteristics of the Patients Studied

Pt	HR (beats/min)	SAP (mm Hg)	PAP (mm Hg)	CO (liters/min)	TSR (units)	TPR (units)	SV (ml/beat)
1	87	78	65	2.74	28	24	31
2	77	99	55	4.31	23	13	56
3	105	102	58	2.63	39	22	25
4	87	90	52	2.65	34	20	31
5	89	63	57	3.75	17	15	42
6	87	87	50	3.75	25	14	43
7	108	81	78	1.27	66	63	12
8	93	96	74	4.21	23	18	46
9	98	88	64	4.18	21	15	43
10	90	86	69	2.08	42	33	23
11	95	83	48	4.08	21	12	43
12	113	78	96	4.42	18	22	39
Mean ± SD	94 ± 10	86 ± 11	64 ± 14	3.34 ± 1.03	30 ± 14	23 ± 14	36 ± 12

All patient data represent the mean of the 6 consecutive hourly determinations.
CO = cardiac output; HR = heart rate; PAP = mean pulmonary artery pressure; SAP = mean systemic arterial pressure; SV = stroke volume; TPR = total pulmonary resistance; TSR = total systemic resistance.

nique. Systemic and pulmonary resistances were calculated in Wood units from standard formulas.

In each case the serial hemodynamic measurements were made with the patient supine and at rest. Although not the same person made these measurements in all patients, the same person made all of the measurements for any given patient over the 6-hour monitoring period. All measurements were made during the daytime and evening hours. The reproducibility and reliability of the thermodilution technique were assessed at both institutions, with simultaneous thermodilution and Fick cardiac output determinations made on a different group of subjects. The correlation between these techniques was highly significant ($r = 0.81$, $p < 0.001$ at the University of Illinois; $r = 0.96$, $p < 0.001$ at the University of Michigan).

Drug testing: After the 6-hour baseline period was established, 8 patients were administered hydralazine and 10 were given nifedipine. Hydralazine was administered as a 0.3-mg/kg slow intravenous infusion or a 50-mg oral dose, with measurements made after 30 minutes and 2 hours, respectively. Nifedipine was administered as either a 10- or 20-mg oral dose, and the measurements made after 90 to 120 minutes. A new control state was established before each drug test.

Data management and statistical methods: For each patient the mean level of each of the 7 hemodynamic variables over the 6 time intervals was computed along with the standard deviation and coefficient of variation. These summary statistics were used to characterize the average levels and variability of the hemodynamic values for each person. Mean levels of each of these individual means, standard deviations, and coefficients of variation were computed over the 12 subjects in the study.

The Pearson product-moment correlation coefficient was used to evaluate the following associations; the variability in PA pressure with cardiac output, the mean level of each hemodynamic variable with the standard deviation, the change in PA pressure and total pulmonary resistance after drug administration with the previously determined coefficient of variation for those variables, the hourly changes in cardiac output with the mean PA pressure and with the total pulmonary resistance. The significance of the effect of drug administration on the PA pressure and the total pulmonary resistance was evaluated by the t test for paired data.

Under the assumption that within each subject repeated determinations of the hemodynamic variables follow a normal distribution, the probability that 2 determinations in the same individual differ by more than a certain percent can be expressed as a function of the specific percent and the coefficient of variation of the distribution of repeat determinations. For a given coefficient of variation and percent, this probability can be obtained numerically by use of the standard normal distribution. Based on the above rationale, we evaluated this

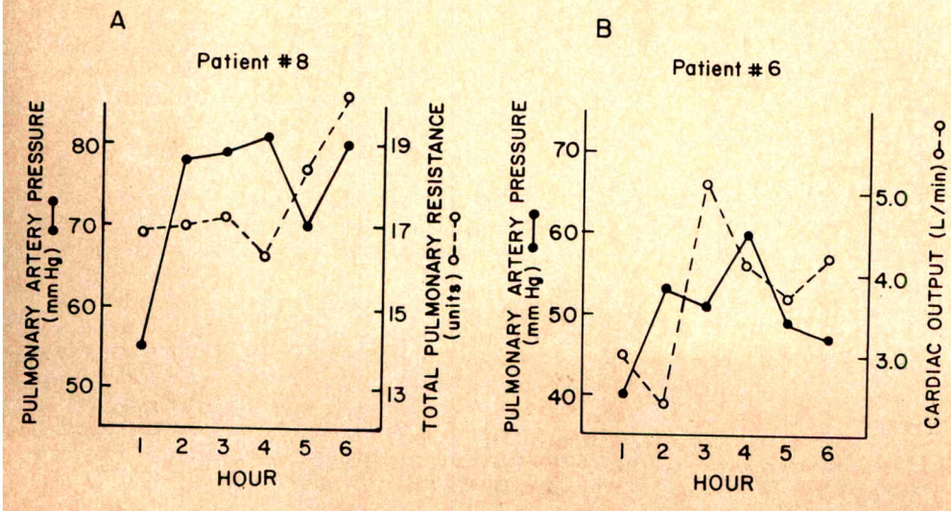

FIGURE 1. The hour-to-hour changes in pulmonary artery (PA) pressure and total pulmonary resistance in patient 8 (**A**) and in PA pressure and cardiac output in patient 6 (**B**). In patient 8, PA pressure increased with essentially no change in pulmonary resistance for the first 4 hours, at which time PA pressure decreased and pulmonary resistance increased dramatically. In the last hour both PA pressure and pulmonary resistance increased together. Patient 6 showed marked variation in PA pressure from hour to hour, without parallel changes in cardiac output. The cardiac output increased substantially between hours 2 and 3 while the PA pressure remained essentially unchanged.

probability using the average coefficient of variation over the 12 subjects as a global estimate of the coefficient of variation.

(Note: In some patients the pulmonary capillary wedge pressure could not always be obtained in consecutive hours. Consequently, total systemic resistance and total pulmonary resistance are being used for statistical analysis in this study. In the cases where left and right ventricular filling pressures were available, we could not find a difference between the amount of variability noted in total systemic resistance and systemic vascular resistance, or total pulmonary resistance and pulmonary vascular resistance.)

Results

Hemodynamic characteristics (Table I): The subjects in the study had advanced PPH as evidenced by the elevated mean PA pressures (64 ± 14 mm Hg) and mean total pulmonary resistance (23 ± 14 units), and reduced cardiac outputs (3.3 ± 1.0 liters/min). The lowest mean PA pressure of any patient in the study was 48 mm Hg, and the lowest total pulmonary resistance was 13 Wood units.

Magnitude of spontaneous variability: Hour-to-hour changes in the hemodynamic values were recorded. The mean levels with the corresponding mean coefficients of variation over the 12 subjects are shown in Table II. In most cases there were unpredictable swings from hour to hour, rather than gradual changes over the 6-hour period. For example, patient 8 had a mean PA pressure rise from 55 to 78 mm Hg, a 42% increase in 1 hour, and patient 6 had a change in cardiac output from 2.4 to 5.1 L/min, a 111% increase in 1 hour, without apparent cause (Fig. 1). Although the changes in pressures seen were not necessarily directly proportional to, or inversely related to the changes in flow in each case, those patients with the greatest variability in their PA pressures also had the most variability in their cardiac outputs ($r = 0.685$, $p = 0.02$) (Fig. 2).

The distribution of the variability in the patients studied was examined to see if it was random. Values of the coefficient of variation of the PA pressures and the pulmonary resistances for each patient are shown in Figure 3. The amount of variability did not appear to be skewed because of patients who were obvious outliers of the group.

Relation between variability and severity of the disease: We examined whether there was an association between the amount of hemodynamic variability and the severity of the disease. There was a significant correlation ($p < 0.01$) between the mean value for total pulmonary resistance and the standard deviation over the 6-hour period ($r = 0.91$), suggesting that patients with higher values for total pulmonary resistance have

TABLE II Hemodynamic Variability Observed over 6 Consecutive Hours and 95% Confidence Limits for Drug Effect in 1 Patient

	Mean Level (n = 12)	Mean CV (n = 12)	% Change for 95% CL
Heart rate (beats/min)	94 ± 10	6.7 ± 2.4	17
Systemic arterial pressure (mm Hg)	86 ± 11	6.8 ± 3.1	17
Pulmonary artery pressure (mm Hg)	64 ± 14	8.4 ± 3.8	22
Cardiac output (liters/min)	3.3 ± 1.0	10.7 ± 5.7	29
Total systemic resistance (units)	30 ± 14	13.9 ± 7.8	39
Total pulmonary resistance (units)	23 ± 14	12.9 ± 6.9	36
Stroke volume (ml/beat)	36 ± 12	12.6 ± 6.4	35

CL = confidence limits; CV = coefficient of variation.

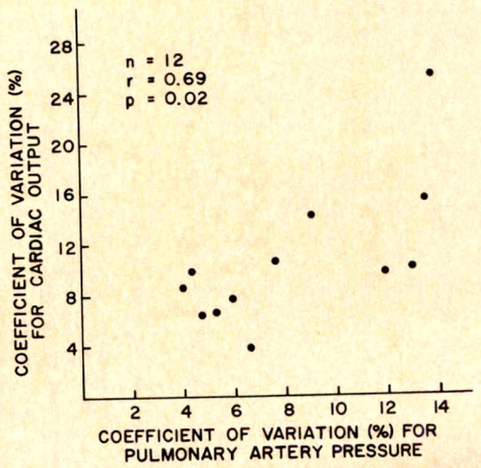

FIGURE 2. Relation between the amount of variability (coefficient of variation) in cardiac output and pulmonary artery pressure. The patients with the greatest amount of variability in pulmonary artery pressure also manifest the greatest amount of variability in cardiac output as determined by hourly measurements.

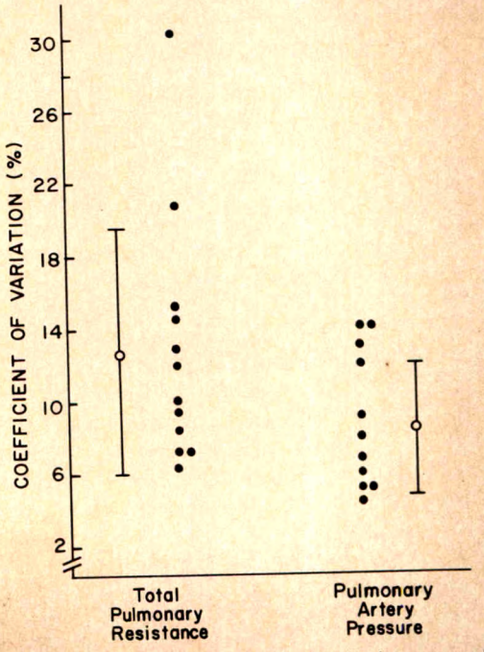

FIGURE 3. The coefficient of variation for total pulmonary resistance and mean pulmonary artery pressure for each of the 12 patients in the study. These values were distributed fairly evenly in the study group.

TABLE III Relation Between the Hourly Measurements in Pulmonary Artery Pressure and Pulmonary Resistance with the Corresponding Cardiac Outout

Pt	Correlation Coefficient (r)	
	PAP vs CO	TPR vs CO
2	0.33	−0.85*
2	0.45	−0.44
3	−0.63	−0.94*
4	0.36	−0.63
5	0.84	−0.92*
6	0.23	−0.83*
7	0.76	−0.93*
8	0.84*	−0.38
9	0.27	−0.38
10	−0.56	−0.91*
11	−0.70	−0.92*
12	0.02	−0.76

* $p < 0.05$.
CO = cardiac outout; PAP = mean pulmonary artery pressure; TPR = total pulmonary resistance.

the most spontaneous hemodynamic variability. This was true for the total systemic resistance (r = 0.78) as well, but not for any of the other measured variables.

Relation between pulmonary blood flow and the corresponding pulmonary artery and pulmonary resistance: The association between the hourly determinations of pulmonary blood flow (cardiac output) and the corresponding mean PA pressure and total pulmonary resistance was analyzed (Table III). A positive linear relation between cardiac output and PA pressure was found in only 1 patient. However, a linear relation was noted between increasing cardiac output and a decreasing pulmonary resistance in 7 of the 12 patients studied. In no patient was an association found between an increasing cardiac output and an increasing pulmonary resistance. Nonlinear relations were not tested.

Spontaneous variation and drug responsiveness: The acute effect of vasodilator administration in the patients studied after the 6 hours of baseline measurements were obtained and analyzed. Hydralazine resulted in an 8% increase in the mean PA pressure and a 16% reduction in pulmonary resistance in the 8 patients tested. Neither of these changes was statistically significant. Nifedipine resulted in 7% reduction in PA pressure and a 25% reduction in pulmonary resistance. Both of these changes were significant (Table IV). There was no correlation between the change in pulmonary resistance or mean PA pressure from administration of either nifedipine or hydralazine and the amount of variation noted to occur spontaneously in these patients.

Magnitude of change required to be attributed to drugs effect: The percentage change in any specific hemodynamic variable that would have to be observed in order for it to be attributed to a drug effect with reasonable confidence, in light of the spontaneous variability that was noted, was derived. A table was constructed that illustrates the percentage change required, based on a 95% confidence level, and the coefficient of variation as determined from this group of patients (Table II). A reduction in mean PA pressure of 22% based on 1 control and 1 postdrug determination, or a reduction in total pulmonary resistance of 36% is required in order to be confident that a vasodilator drug was clearly effective in a single patient. When drugs are evaluated in groups of patients, however, significant drug effects can be determined from parametric testing, as it is assumed that the effect of variability within the group will cancel itself out. Thus, although individual patients tested with nifedipine had changes in PA pressure of less than 22%, the drug had a significant effect on the group as determined by the Student *t* test.

Discussion

The occurrence of spontaneous changes in pulmonary resistance in patients with PPH have been described.[6] A previous study of captopril therapy in PPH showed how the presence of spontaneous hemodynamic variability made the assessment of drug effects difficult.[8] Spontaneous variability is a feature of biologic systems and pathologic manifestations of disease,[9–11] and its quantification is critical in the assessment of drug therapies.[8,12]

This study confirms that hour-to-hour changes in systemic and PA pressure and cardiac output often occur in patients with PPH. This variability may be of similar magnitude in both the systemic and pulmonary circulations, and may be large in some cases. One might question whether the variation observed was due to technical laxity by the personnel making the measurements, but if it were, it should have then been approximately the same from patient to patient. Patients who had the greatest amount of change in their PA pressures also had the greatest change in cardiac output, which is consistent with biologic behavior. Samet and Bernstein[13] suggested that a large amount of variability in pulmonary resistance is indicative of active and reversible vasoconstriction, and is a feature of less advanced disease. However, the amount of variability correlated with the level of total pulmonary resistance, which suggests that variability is a feature of advanced PPH.

We studied the relation between the changes in pulmonary blood flow and the corresponding changes in PA pressure and pulmonary resistance to see if we could determine the mechanisms of variability. In 1 patient the PA pressure increased with the cardiac output, whereas the pulmonary resistance did not, a response characteristic of normal subjects. In 7 patients the pulmonary resistance fell as pulmonary blood flow increased, with the changes in PA pressure independent of the pulmonary blood flow. This would suggest that changes in the cross-sectional area of the pulmonary vascular bed were occurring. Whether this was a result of changing distensibility in the resistance vessels or of vessel recruitment is not known. However, only linear relations between flow and pressure, and flow and resistance were studied and the range of changes in flow was narrow.

TABLE IV Relation Between Vasodilator Drug Testing and Spontaneous Variability

	Hydralazine						Nifedipine					
	PA Pressure (mm Hg)			Pulmonary Resistance (units)			PA Pressure (mm Hg)			Pulmonary Resistance (units)		
Pt	C	Rx	CV	C	Rx	CV	C	Rx	CV	C	Rx	CV
1	64	56	4.5	23	18	8.2	61	58	4.5	23	20	8.2
2	51	58	13.0	15	14	12.5	42	38	13.0	9	7	12.5
3	55	60	5.9	19	19	12.4	61	60	5.9	24	20	12.4
4	55	58	11.9	23	13	14.6	51	47	11.9	21	16	14.6
5	50	70	4.3	18	21	6.4	52	54	4.3	18	17	6.4
6	40	48	13.8	13	9	30.2	53	55	13.8	10	9	30.2
7	...	...	...	...	...	...	78	74	9.2	55	32	20.9
8	80	76	13.6	20	14	8.3	70	59	13.6	16	11	8.3
11	43	48	7.6	9	10	15.4	48	43	7.6	12	8	15.4
12	...	...	...	...	...	...	93	76	5.3	19	12	8.8
Mean ± SD	55 ± 13	59 ± 10	8.5	18 ± 5	15 ± 4		61 ± 16	56 ± 12		21 ± 13	16 ± 8	
p value		NS			NS			<0.05			<0.05	
r			−0.13			0.32			−0.08			0.05

C = control value before drug administration; CV = coefficient of variation for the 6-hour baseline determination; NS = not significant; PA = pulmonary artery; Rx = value after drug administration; SD = standard deviation.

It has also been suggested that the presence of spontaneous variability in pulmonary vascular resistance predict success with vasodilators in treating patients with pulmonary hypertension.[6,14] We could not correlate the amount of variability to drug responsiveness with nifedipine or hydralazine. Neither were the patients with the greatest reduction in pulmonary resistance from the drugs the same ones that appeared to have the most spontaneous change in pulmonary vascular tone. A modest but significant reduction in PA pressure (5 mm Hg) and pulmonary resistance (5 units) occurred with nifedipine, but not with hydralazine.

Because the values were measured every hour, the possibility exists that a drug response measured at an interval of less than 60 minutes may be less influenced by spontaneous variability, or that variability may have a greater influence in the assessment of chronic therapy made over weeks or months. Although these patients were randomly referred to us for study, it is also possible that variability may not be as evident in other patients with pulmonary hypertension, particularly from other causes.

When one reviews previous studies evaluating vasodilator drugs in PPH, one is impressed by the marked lack of uniform criteria that have been used in deciding what magnitude of change determines a beneficial drug response. Based on the patients in this study, we constructed a table that indicates the amount of change required in order to achieve 95% confidence that a hemodynamic effect was drug-related. In an individual patient there must be a relatively large change (e.g., 22% in mean PA pressure and 36% in pulmonary resistance) in order for it to be attributed (with 95% confidence) to a drug effect rather than spontaneous variability (Table II). This must be considered before one makes conclusions about drug effects in individual patients with PPH.

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Acute Effects of Alcohol on Left Ventricular Function in Healthy Subjects at Rest and During Upright Exercise

HENNING KELBAEK, MD, THOMAS GJØRUP, MD, INGELISE BRYNJOLF, MD, NIELS JUEL CHRISTENSEN, MD, and JOHN GODTFREDSEN, MD,
With the technical assistance of BIRGIT VESTERGAARD

Six healthy men, aged 23 to 30 years, were studied by radionuclide angiocardiography at rest and at 2 submaximal exercise levels in the upright position during increasing alcohol intoxication. At light intoxication (serum ethanol 23 mmol/liter), the median value of left ventricular (LV) ejection fraction (EF) at rest decreased by 5%. At heavy intoxication (serum ethanol 45 mmol/liter), the median LVEF decreased at rest by 11% and during 75% submaximal exercise by 6%, heart rate at rest increased (median 81 vs 62 beats/min), and systolic blood pressure decreased during 50% submaximal exercise (median 145 vs 163 mm Hg). No significant changes of plasma epinephrine concentrations were recorded, whereas plasma norepinephrine concentrations were increased by 24% at rest during light intoxication and by 30 to 38% during heavy intoxication. No changes of LVEF and plasma catecholamine levels were recorded after ingestion of isovolumic, isocaloric drinks as compared with values obtained before intake. Thus, influences of ingestion per se and repeated investigations of LV function were excluded. These findings suggest that in healthy subjects alcohol intoxication causes a dose-dependent impairment of cardiac contractility. Compensatory mechanisms may account for a reduced influence during exercise.

(Am J Cardiol 1985:55:164–167)

There is evidence that ethanol has both acute and chronic toxic effects on cardiac function, and that changes in cardiac metabolism and hemodynamic alterations are caused by alcohol exposure.[1–3] Although the prevailing view has been that intoxication causes depression of myocardial contractility, studies of acute hemodynamic effects of ethanol in normal subjects have yielded conflicting results,[4–11] probably as a result of different study designs and use of clinical parameters of varying validity as to cardiac function.

Multiple gated cardiac blood pool imaging performed by radionuclide angiocardiography is valuable in the detection of ventricular dysfunction.[12] In addition, the alteration of left ventricular (LV) ejection fraction (EF) during exercise is a sensitive test for detecting latent heart failure.[13] The present study evaluates changes of LVEF at rest and during submaximal exercise in healthy subjects at increasing levels of alcohol intoxication. Plasma catecholamine levels were measured to clarify the significance of the autonomic nervous system masking intrinsic myocardial depression by ethanol.[9]

From the Department of Clinical Physiology and Nuclear Medicine, Department of Cardiology and Medical Endocrinology, Herlev Hospital, University of Copenhagen, Herlev, Denmark. This study was supported by the Danish Medical Research Council and the Danish Heart Foundation, Copenhagen, Denmark. Manuscript received June 27, 1984; revised manuscript received September 10, 1984, accepted September 11, 1984.

Address for reprints: Henning Kelbæk, MD, Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark.

Methods

Subjects: Six healthy, nonsmoking men, aged 23 to 30 years (median 25) (medical students and physicans), with a daily alcohol consumption of less than 25 g (0.9 oz), entered the study. The median weight was 70 kg (range 60 to 85). The study protocol was approved by the local scientific ethical committee, and each subject gave informed consent.

Procedure: Each subject was studied twice, with an interval of at least 1 week. The subjects were familiar with the investigation schedule when they arrived in the laboratory after at least 6 hours of fasting. Investigations were performed before and during light and heavy alcohol intoxication in the upright position at rest and during steady-state submaximal bicycle exercise corresponding to 50 and 75% of the maximal work capacity as assessed by Åstrand.[14] Data recorded were heart rate (HR), auscultatory blood pressure (BP), precordial electrocardiographic leads, and radionuclide angiocardiography. Venous blood samples were drawn for determination of serum ethanol and plasma catecholamine levels. After initial baseline measurements at rest and during exercise, the

subjects rested for 10 minutes. During the following 20-minute period 0.9 g of ethanol per kilogram body weight was administered in the form of 80-proof whiskey with an equal volume of chilled water. The subjects were thereafter allowed to rest for 30 minutes before data were acquired at rest and during exercise. After a rest period of 10 minutes, an additional amount of whiskey and water corresponding to 0.9 g of ethanol per kilogram was administered and data acquisition was repeated; serum ethanol levels were recorded 30 min after termination of the last exercise performance.

The control study was performed in each subject on another day. The entire investigation program as outlined above was carried out with the exception that ethanol was replaced by an isocaloric, isovolumic solution of a nonalcoholic drink.

Radionuclide angiocardiography: Radionuclide angiocardiography was performed after in vitro labeling of autologous red blood cells with approximately 30 mCi of technetium-99m pertechnetate. Data were collected by aid of an image magnifier with a gamma scintillation camera (PHO, ZLC, Siemens). LVEF was determined in the left anterior oblique projection with a caudal tilt of 5 to 10°, allowing an optimal outlining of the left ventricle. Multiple electrocardiographic-gated equilibrium blood scintigrams were achieved by division of each cardiac cycle into 16 frames. Activity was compiled over 800 to 1,000 beats. Data were acquired in 64 × 64 frame format, and regions of interest were delineated in 128 × 128 frame format of end-diastole and end-systole with a light pen from the isocount contour. Background was defined as an area just inferior and lateral to the apex of the heart. LVEF was calculated as [(end-diastolic counts − end-systolic counts)/end-diastolic counts], with all counts corrected for background activity. End-diastolic and end-systolic areas were determined by counting the number of pixels comprising the area delineated by the light pen.

Plasma catecholamine levels: Plasma epinephrine and plasma norepinephrine concentrations were determined by isotope derivative assay.[15]

Serum ethanol levels: Serum ethanol concentrations were determined by the gas chromatographic method.

Statistical analysis: All data acquired during ethanol intoxication were compared with the appropriate values obtained before alcohol intake. Similarly, data acquired after intake of isocaloric drinks were compared with the values before ingestion.

Statistical analyses were performed by means of the Wilcoxon rank-sum test for paired data. A p value <0.05 was regarded as the level of significance.

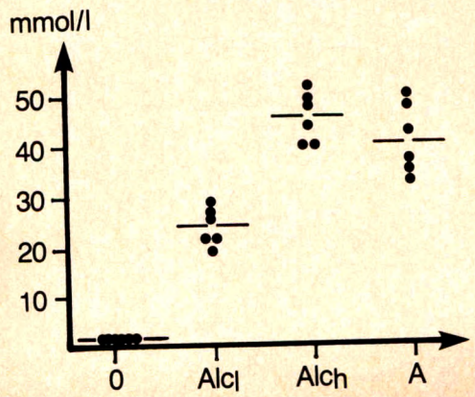

FIGURE 1. Serum ethanol levels before alcohol intake (0), during light (Alc_l) and heavy (Alc_h) intoxication, and 30 minutes after (A) cessation of measurements.

TABLE I Heart Rate and Blood Pressure at Rest and at Submaximal Exercise Before and During Light and Heavy Alcohol Intoxication

	Rest		Submaximal Exercise I			Submaximal Exercise II		
	HR (beats/min)	BP (mm Hg)	Workload (kpm/min)	HR (beats/min)	BP (mm Hg)	Workload (kpm/min)	HR (beats/min)	BP (mm Hg)
0	62	120/80	640	123	163/80	825	152	180/85
	(54–70)	(115–130/70–95)	(450–90)	(120–140)	(145–190/75–90)	(675–1200)	(146–171)	(150–210/70–100)
Alc_l	68	118/83	. . .	129	170/83	. . .	158	185/80
	(68–100)	(100–130/55–90)		(120–151)	(140–180/70–100)		(145–168)	(140–200/80–90)
Alc_h	81*	110/80	. . .	136	145/80*	. . .	163	180/80
	(72–115)	(90–120/60–100)		(115–160)	(130–170/75–90)		(140–170)	(140–200/70–100)

* $p < 0.05$ compared with 0 value.
Values are medians; ranges are listed in parentheses.
Submaximal exercise I and II represent 50% and 75%, respectively, of maximal work capacity.
Alc_h = heavy alcohol intoxication; Alc_l = light alcohol intoxication; BP = blood pressure; HR = heart rate; 0 = before alcohol intoxication.

TABLE II Left Ventricular Ejection Fraction Before and During Light and Heavy Alcohol Intoxication in Six Healthy Subjects at Rest and at 50% and 75% of Maximal Work Capacity

Alcohol Intoxication (Intake of Isocaloric Drink)	Rest	Submax. Ex. I	Submax. Ex. II
0			
Median	67 (67)	73 (71)	75 (76)
Range	58–75(53–72)	68–79(65–81)	69–81(67–81)
AIc_l			
Median	62* (65)	72 (72)	70 (75)
Range	55–70(54–73)	62–79(61–80)	64–79(65–80)
AIc_h			
Median	56* (63)	70 (73)	69* (75)
Range	52–69(56–72)	62–79(66–77)	63–79(68–84)

* $p < 0.05$ compared with 0 value.
Values in parentheses are control values before and after intake of isovolumic, isocaloric drinks.
AIc_h = heavy alcohol intoxication; AIc_l = light alcohol intoxication; 0 = before alcohol intoxication; Submax. Ex. I = 50% of maximal work capacity; Submax. Ex. II = 75% of maximal work capacity.

Results

Median serum ethanol concentrations at light and heavy intoxication of the subjects were 23 mmol/liter (106 mg/100 ml) and 45 mmol/liter (207 mg/100 ml), respectively (Fig. 1). All data acquired during ethanol intoxication were compared with the values obtained before alcohol intake. At light intoxication, no significant changes in HR or BP were recorded. At heavy intoxication HR at rest was increased (by 81 vs 62 beats/min $p < 0.05$), while systolic BP during 50% submaximal exercise was decreased (145 vs 163 mm Hg, $p < 0.05$) (Table I). A decrease in LVEF at rest was recorded at light intoxication (median 5%), while at heavy intoxication a decrease in LVEF was recorded both at rest (median 11%) and during 75% submaximal exercise (median 6%) (Table II) ($p < 0.05$).

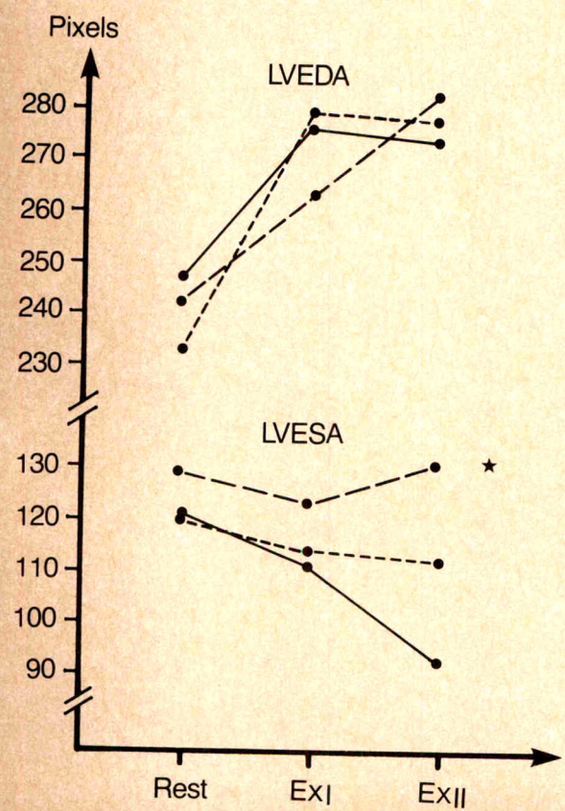

FIGURE 2. Left ventricular end-diastolic areas (LVEDA) and end-systolic areas (LVESA) at rest and during 50% (Ex_I) and 75% (Ex_{II}) submaximal exercise before alcohol intake (●——●), at light (●- - -●), and at heavy (●– — –●) intoxication. * $p < 0.05$ compared with before alcohol intake.

No significant alterations of end-diastolic areas due to ethanol intoxication were recorded (Fig. 2). End-systolic volume tended to increase, but only at heavy intoxication during 75% submaximal exercise did the end-systolic dilation reach significance (median change of LV end-systolic area 141% of the value before intoxication, $p < 0.05$) (Fig. 2).

No significant changes due to ingestion of isovolumic, isocaloric drinks were recorded in any of the investigation variables.

A median increase of 24% ($p < 0.05$) was recorded in plasma norepinephrine concentration at rest during light alcohol intoxication. At heavy intoxication an increase was recorded at rest (median 38%) as well as during 50% and 75% submaximal exercise (median 35% and 30%, respectively, all $p < 0.05$). No significant changes were recorded in plasma epinephrine concentration due to alcohol intoxication (Table III).

Discussion

The results of the present study suggest that alcohol intake causes an acute dose-dependent reduction of LVEF at rest. Similar findings have been reported in experimental[16–19] and clinical[6,7,20] studies. However, it has not been demonstrated previously that a more pronounced adverse effect of ethanol on cardiac performance is recorded at rest than during exercise. This finding indicates that during exercise, compensatory mechanisms are activated to counterbalance the LVEF-reducing effect of ethanol. In normal subjects, an increase of end-diastolic volume with a concomitant decrease of end-systolic volume is recorded during upright exercise.[21] The results of the present control study are in accordance with this concept. During ethanol intoxication, however, LV end-systolic volume as in-

TABLE III Plasma Catecholamines at Rest and at Submaximal Exercise Before and During Light and Heavy Alcohol Intoxication

	Epinephrine (ng/ml)			Norepinephrine (ng/ml)		
	Rest	Submax. Ex. I	Submax. Ex. II	Rest	Submax. Ex. I	Submax. Ex. II
0	0.08 (0.05–0.20)	0.12 (0.08–0.17)	0.16 (0.09–0.53)	0.29 (0.21–0.49)	0.46 (0.38–0.87)	0.83 (0.69–2.18)
Alc_l	0.07 (0.04–0.11)	0.10 (0.07–0.16)	0.12 (0.10–0.35)	0.36* (0.25–0.58)	0.51 (0.35–1.01)	0.83 (0.51–2.13)
Alc_h	0.08 (0.03–0.59)	0.16 (0.07–0.41)	0.20 (0.11–0.57)	0.40* (0.26–0.86)	0.62* (0.40–1.54)	1.08* (0.82–3.21)

* $p < 0.05$ compared with 0 value.
Values are medians; ranges are in parentheses.
Abbreviations as in Table II.

dicated by pixel area tended to increase, while a reduction of the end-systolic volume during exercise failed to appear (Fig. 2), suggesting that ethanol causes a reduction in cardiac contractility. At heavy intoxication, systolic BP was maintained when LVEF was decreased, indicating an inverse correlation between these variables. Alcohol may have effects on BP during exercise independent of its effects on cardiac contractility. Despite a tendency of LV end-diastolic volume at rest to decrease (Fig. 2), no significant alcohol-induced changes of end-diastolic areas were recorded.

Kupari et al[10] reported echocardiographic findings indicating augmented LV function during the early stage of alcohol intoxication. Changes of LVEF and end-systolic volume recorded in the supine position were small and short-lived, however, and the major reason for the increase in cardiac output was an increase of heart rate. These findings are in accordance with other controlled studies demonstrating no alterations or even slight improvements of LV performance during alcohol intoxication.[4,5,22] In those studies, however, LV stroke volume was taken as an index of LV performance and LVEF was not determined.

In a study by Child et al,[9] no changes of LV function as assessed by systolic time intervals and echocardiography could be demonstrated at a mean blood ethanol level of 110 mg/100 ml (23.9 mmol/liter) in healthy subjects. However, ethanol plus autonomic blockade produced with intravenous propranolol and atropine revealed a decrease in mean velocity of circumferential fiber shortening and an increase in preejection period–LV ejection time ratio. Their suggestion that the ethanol-induced negative inotropic effect is masked by sympathetic nervous system discharge was supported by the present findings, since the reduction of LVEF was accompanied by an increase of plasma norepinephrine.

From the present study we conclude that in healthy subjects; (1) ethanol produces a decrease in cardiac contractility, resulting in a reduced LVEF; (2) the LVEF reduction is dose-dependent; and (3) the changes are most pronounced at rest. Whether the increase in the plasma norepinephrine level is compensatory or a direct ethanol effect on sympathetic nerve endings remains unsettled, as does the inotropic role of catecholamine levels during alcohol intoxication.

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Diastolic Time During Recovery from Upright Exercise in Persons Without Heart Disease

TETSURO SUGIURA, MD, TOSHIJI IWASAKA, MD, YOSHINORI L. DOI, MD, BRUCE G. HAFFTY, MD, MITSUO INADA, MD, and DAVID H. SPODICK, MD, DSc

To assess the relation between heart rate and diastolic time (cardiac cycle minus electromechanical systole) during the recovery period from upright exercise, 12 normal volunteers were studied immediately after and 2 and 5 minutes after exercise in the upright position. Although heart rate was significantly lower at 5 minutes compared with 2 minutes after exercise (106 vs 116 beats/min), there was significant shortening of diastolic time (from 251 to 230 ms) and total diastole per minute (from 28,634 to 24,220 ms/min). The explanation of this phenomenon appears to be disproportionate lengthening of diastolic time at 2 minutes after exercise, which must represent physiologic response due to increased left ventricular filling as well as continuing adrenergic effects, which would be diminished at 5 minutes. This lengthening of diastolic time also would maintain decreased subendocardial blood flow caused by increased end-diastolic volume. (Am J Cardiol 1984;54:168–170)

Diastolic time (cardiac cycle minus electromechanical systole) is well known to have a nonlinear relation with heart rate (HR); it increases with decreasing HR. This relation has been determined with various medications,[1] but its consistency during the recovery period from exercise has not been elucidated. This study examines the HR-diastolic time (DT) relation during the recovery period after exercise.

Methods

Subjects: We studied 12 normal volunteers, aged 24 to 49 years, who fulfilled the following criteria: (1) normal medical history and no abnormalities found on physical examination, chest x-ray film and electrocardiogram, and (2) achieving age-predicted submaximal HR with negative electrocardiographic responses.

Recordings: Subjects were studied in the postabsorptive state. Data for systolic time intervals were recorded from the ear densitograph pulse derivative and the electrocardiogram.[2–5] The ear densitograph pulse derivative, because of the demonstrated stability of the pulse transmission time, is a reliable, reproducible pulse measurement for determining all the systolic time intervals in various conditions.[3–5]

Ear densitograms were obtained with a Hewlett Packard 780-10 photoelectric earpiece, modified and filtered through a Hewlett Packard 7712 recording system, as previously reported.[6] Recordings were made on a Cambridge 3044B 3-channel stress test system at a paper speed of 100 mm/s.

Procedure: Subjects exercised on a Quinton Type 18-54 treadmill without interruption to their submaximal HR. Recordings were made immediately after and 2 minutes and 5 minutes after exercise and recovery with the patient in the sitting position. With each of these recordings cuff blood pressure was measured.

Measurements: Methods for measuring HR, preejection period (PEP) and left ventricular ejection time (LVET) are described elsewhere.[3,5] DT was calculated as cardiac cycle (RR) minus electromechanical systole (QS_2): QS_2 = PEP + LVET. Measurements of HR and systolic time intervals were aided by a digitizing technique using a Summagraphics digitizer coupled to a DEC-20 computer, and were calculated from means of 5 consecutive beats for each of the recordings. Total diastole per minute (DT × HR) was also evaluated.

Statistical analysis: The *t* test for paired sample was used to compare each postexercise value. The other systolic time intervals, PEP, LVET and their ratio were also calculated.

Results

Results are summarized in Figure 1 and Table I. **Responses immediately after and 2 minutes after exercise:** HR and double product (systolic blood pressure × HR) decreased significantly during this period ($p < 0.001$ and $p < 0.001$, respectively), while QS_2 lengthened significantly ($p < 0.001$). There was significant lengthening of DT and total diastole per minute during this period ($p < 0.001$).

Responses 2 and 5 minutes after exercise: Despite a significant decrease in HR, there were "paradoxical"

From the Second Department of Internal Medicine, Kansai Medical University, Fumizono Cho Moriguchi City, Japan, and the Division of Cardiology, St. Vincent Hospital, Worcester, Massachusetts. Manuscript received May 31, 1984; revised manuscript received September 11, 1984, accepted September 13, 1984.

Address for reprints: Tetsuro Sugiura, MD, Coronary Care Unit, Kansai Medical University, 1 Fumizono Cho Moriguchi City, Osaka, Japan 570.

TABLE I Responses During Recovery Period of Treadmill Exercise

	HR			DT			HR × DT			QS_2			DP		
	I	2	5	I	2	5	I	2	5	I	2	5	I	2	5
Mean	163	116	106	143	251	230	23270	28634	24220	226	273	339	28673	17769	13965
SD	11	13	10	17	47	34	2414	2999	2000	22	32	31	3340	2775	2249
SE	3	4	3	5	14	10	697	866	577	6	9	9	964	801	649
p values															
I to 2 min	<0.001			<0.001			<0.001			<0.001			<0.001		
2 to 5 min	<0.001			<0.005			<0.001			<0.001			<0.001		
%Δ	−29	−35		+76	+61		+23	+4		+21	+50		−38	−51	

DP = double product; DT = diastolic time; 5 = 5 minutes after exercise; HR = heart rate; I = immediately after exercise; %Δ = percent change from value immediately after exercise; QS_2 = electromechanical systole; SD = standard deviation, SE = standard error of the mean; 2 = 2 minutes after exercise.

shortening of DT and total diastole per minute (Fig. 1, Table I). Double product decreased and QS_2 increased significantly during this period ($p < 0.001$ and $p < 0.001$, respectively).

PEP, LVET and PEP/LVET progressively increased during the recovery period (Table II).

TABLE II Changes in Systolic Time Intervals (ms) After Exercise

	Immediate	2 min	5 min
PEP	54 ± 7	71 ± 11	98 ± 10
LVET	172 ± 19	202 ± 27	238 ± 22
PEP/LVET	31 ± 5	36 ± 5	41 ± 5

Values are mean ± standard deviation.
LVET = left ventricular ejection time; PEP = preejection period.

Discussion

Although HR decreased throughout the recovery from exercise, DT shortened significantly at 5 minutes after exercise, which was opposite to the expected relation. Compared with HR immediately after exercise, a significant decrease in HR (lengthening of RR interval) and lengthening of QS_2 were seen as well as lengthening of DT at 2 minutes after exercise. At 5 minutes after exercise, despite lengthening of the RR interval and QS_2, DT shortened significantly compared to 2 minutes after exercise. An increase in HR (shortening of RR interval) or lengthening of QS_2 will cause shortening of DT. Shortening of DT during 2 minutes to 5 minutes after exercise was accompanied by a decrease in HR and lengthening of QS_2. Possible explanations for the shortening of DT are: (1) DT at 2 minutes after exercise was disproportionately prolonged (QS_2 shortened) and (2) DT at 5 minutes after exercise was disproportionately shortened (QS_2 prolonged) for a given HR. Despite the smaller reduction of HR (29%) at 2 minutes compared with 5 minutes (35%) after exercise, percent lengthening of DT at 2 minutes (76%) was larger than 5 minutes after exercise (61%). In addition, total diastolic time per minute at 2 minutes after was significantly longer than immediate or 5 minutes after exercise. Thus, for this phenomenon, the primary factor appears to be the disproportionate lengthening of DT at 2 minutes after exercise, causing a fundamental change in the HR-DT relation.

An increase in cardiac function associated with increase in end-diastolic diameter or stroke volume during the recovery phase, has been postulated.[7–10] In our patients, reduction in double product (less oxygen demand)[11] and lengthening in QS_2 (less sympathetic stimulation to the heart)[12,13] were seen throughout the recovery period. Therefore, this disproportionate prolongation of DT at 2 minutes after exercise, while related to continuing adrenergic effects on QS_2 (i.e., shortening) must be related to elevated left ventricular filling (faster decrease in HR than venous return) at 2

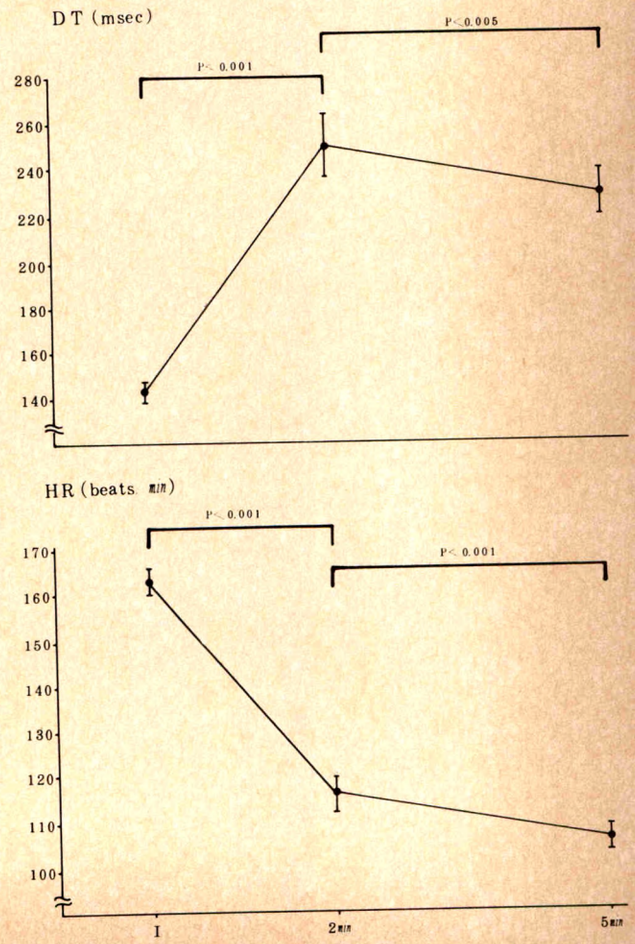

FIGURE 1. Behavior of diastolic time (DT) and heart rate (HR) during early recovery period of treadmill exercise. Values are mean ± standard error of the mean. I = immediately after exercise; 2 min and 5 min = 2 and 5 minutes after exercise.

minutes, diminished adrenergic effects on duration of systole (QS_2) or both. It is also a desirable mechanism to maintain decreased subendocardial coronary blood flow caused by an increase in end-diastolic volume.[9,14]

This direct relation of DT and HR from the second to the fifth minute of the recovery phase after treadmill exercise observed in this study implies that this relation is a physiologic phenomenon, despite the general nonlinear, inverse relation of DT with HR.

The changes (progressive increases) in PEP, LVET and PEP/LVET (Table II) represent the expected postexercise restitution changes.[5,7,15,16]

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Radiation Exposure and Protection in Cardiac Catheterization Laboratories

STEPHEN W. MILLER, MD, and FRANK P. CASTRONOVO, Jr., PhD

Cardiac catheterization with angiography can deliver the greatest dose of x-radiation of any diagnostic medical examination. The physicians and technologists in the angiography room receive low-level scattered radiation over a period of months to decades. Although the radiobiology is complex, the physicians who perform cardiac catheterization should be familiar with the potential genetic and somatic effects of radiation and with the methods to reduce or eliminate x-ray exposure. The aim of radiation protection criteria is to reduce the risk of cancer death to less than the fatality risk for other occupations regarded as safe. This report is a review of the literature relating to radiation exposure and protection in cardiac catheterization laboratories. Catheterization personnel have control over the time duration of exposure, placement of technologists, shielding, location of equipment and monitoring of dose received.

(Am J Cardiol 1985;55:171–176)

Cineangiography is used daily for the evaluation of patients with heart disease. Cineangiography and fluoroscopy combined make cardiac catheterization the producer of the largest x-ray dose of any examination in diagnostic radiology.[1,2] The use of x-rays in the catheterization laboratory is generally acceptable because the expected benefits derived from the angiography are considered to outweigh the risks. What are the risks from radiation exposure in the cardiac catheterization laboratory and how can they be reduced?

Sources and Amounts of Radiation Exposure

Numerous studies have documented the radiation exposure to patients and personnel during cardiac catheterization procedures.[3–10] The amount of radiation received varies widely among laboratories and depends on the type of equipment used, the operating techniques and length of the procedure, the shielding of the x-ray beam, and the administrative procedures regarding the placement of personnel. The amount of radiation received from a given medical procedure can be compared with that received annually from natural and artificial sources (Table I).

A nationwide survey by the Bureau of Radiological Health estimated that 65% of the people in the United States were exposed to medical or dental x-rays in 1970.[11] Studies have shown that the largest source of exposure of the population to man-made radiation is medical and dental radiologic procedures.[11,12] The mean dose rates to patients and physicians during cardiac catheterization are listed on Table II. These values are a summary from different types of room installations and procedure times. Most of the patient dose for cardiac procedures is delivered directly by the beam to the thoracic area. Patient-scattered radiation affects mainly the thyroid in adults but also the eye and abdomen in the child. Personnel exposures result from the primary x-ray beam being scattered by tissue in the patient's thorax. The chest, thyroid and eyes receive most of the scattered radiation (Fig. 1).

Genetic and somatic effects of low radiation doses have been the subject of many reviews.[13–16] Genetic effects are those that affect the germ cells and may be transmitted to the progeny. Somatic effects include malignancies, especially leukemia, cataracts, and developmental abnormalities of children exposed in utero.

The incidence of radiation-induced genetic disorders in humans is uncertain, not only because of the lack of acceptable data but also because of the large number of mutations that are already carried by persons. The incidence of human genetic disorders occurring spontaneously is greater by a factor of 100 compared with that which would additionally occur from parental x-ray exposure.[12] Therefore, the frequency of detectable somatic effects greatly exceeds that resulting from genetic effects.

From the Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts. Manuscript received June 11, 1984; revised manuscript received August 24, 1984, accepted August 27, 1984.

Address for reprints: Stephen W. Miller, MD, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts 02114.

TABLE I Sources of Significant Radiation Exposure*

	Average Dose Rate mrem (mSv)†
Natural background	
Cosmic radiation	28 (0.28)
Terrestrial radiation	15–140 (0.15–1.4)
Internal sources	26 (0.26)
Medical x-rays	
Medical diagnosis	103 (1.03)
Dental diagnosis	3 (0.03)
Other	
Atmospheric weapons tests	4–5 (0.04–0.05)
Brick and masonry buildings	7 (0.07)
Television receivers	0.1–1.5 (0.001–0.015)

* Modified from Reference 12.
† One hundred rem = 1 Sievert (Sv); 1/100 mrem = 1 mSv.

Cancer induction appears to be the most important somatic effect of low-dose ionizing radiation, defined as less than 100 rem (1 Sievert [Sv]). These cancers may be either benign or malignant and are indistinguishable from those occurring naturally. A radiation dose greater than 100 rem (1 Sv) unequivocally is leukemogenic in adults. However, the induction of cancer by lesser amounts of radiation is detectable only by statistical means and cannot be attributed with certainty to a spontaneous occurrence, radiation or some other cause.[14] Cancer occurrence in radiologists has been analyzed over an 80-year period from 1897 to 1977.[17] For radiologists who entered the profession before 1921, when improved radiation protection measures were introduced nationally, there was an excess of cancer deaths compared with physicians in other specialties. For those who entered the profession after 1935, there has been a deficit of cancer deaths relative to other physicians. Because radiation-induced cancers have a latent period of up to 40 years after exposure, one may not conclude that the risk of radiation-induced cancer has been eliminated by modern protective measures. In the diagnostic range of less than 10 rem (0.1 Sv), there are no scientifically well controlled studies to indicate that the incidence of malignant disease is increased in humans.

Cataract production can result from long-term, low-level x-ray exposure.[18] After a latent period of several years, a reasonably defined threshold of about 250 rem (2.5 Sv) results in diffuse cataracts. Smaller opacities have developed in the lenses of mice subjected to only 50 rem (0.5 Sv).[19]

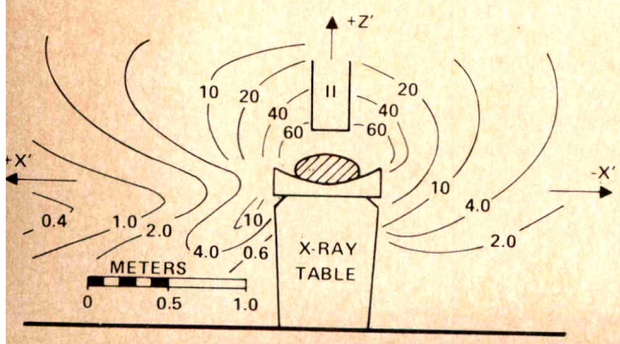

FIGURE 1. Pattern in the vertical plane of exposure values (milliroentgen per hour) during cardiac catheterization. Typical values of 96 kVp, 10 × 10 cm field and 1.95 R/min tabletop exposure rates were used. Reprinted by permission of the American Heart Association from Rueter.[6])

TABLE II Mean Radiation Exposure to Patient and Physician During Cardiac Catheterization*

Site	Mean Dose mrem (mSv)	
	Patient	Physician
Adults		
Eye		20 (0.2)
Thyroid	250 (2.5)	2–16 (0.02–0.16)
Chest	1,100 (11)	500 (5)
Chest (inside apron)		50 (0.5)
Hand		10–30 (0.1–0.3)
Gonads	12 (0.12)	10 (0.1)
Children		
Eye	26 (0.26)	
Thyroid	430 (4.3)	
Chest	7,500 (75)	
Abdomen	150 (1.5)	
Gonads	10 (0.1)	
Comparison Exposures		
Annual cumulative from natural sources		100 (1)
Chest radiography		10 (0.1)
Upper gastrointestinal series		3,000 (30)
Lumbar spine series		3,000 (30)
Pulmonary angiography		15,000 (150)
Chest fluoroscopy		1,000–2,000/min (10–20/min)

* Modified from References 2, 6, 9 and 10.

Personnel Radiation Dose for Cardiac Angiography

The National Council on Radiation Protection has established maximal permissible doses for persons who receive occupational exposure.[20] There are no standards for patients. For personnel working with by-product material (reactor produced), the Nuclear Regulatory Commission has suggested that occupational exposure should be as low as reasonably achievable (ALARA) (Table III). Quarterly exposures in excess of level 1 amounts are reviewed by the radiation safety officer. Level 2 exposures are 3 times those of level 1 and require a written report to the Nuclear Regulatory Commission describing why the high-dose level occurred and steps taken to reduce the dose in the future. At our institution we have extended the ALARA concept to personnel exposure from diagnostic x-rays.

Personnel monitoring of radiation dose is frequently accomplished with a standard film badge. Its proper placement, however, is being debated. One report recommends the badge be worn on the collar of a lead apron, because this part of the body is most likely to receive the greatest proportion of the permissible dose.[21] Other investigators recommend the proper placement of the badge for estimation of whole-body dose to be on the trunk under the apron.[22] Ideally, a second dosimeter could be worn on the collar during fluoroscopic and catheterization procedures, as is the case at our institution. Film badge dosimeters are calibrated to measure dose equivalent in mrem (mSv). Film badge records for

TABLE III Summary of ALARA Guidelines for Limiting Personnel Exposure to Diagnostic Equipment*

Organ	Maximal Permissible Dose (mrem)		ALARA	
	Year	Quarter	10% MPD Level I	30% MPD Level II
Whole body (including gonads, lens of eye, red bone marrow)	5,000	1,250	125	375
Forearms, hands, feet and ankles	75,000	18,750	1,875	5,625
Skin of whole body	30,000	7,500	750	2,250
Pregnant women or employees <18 years of age	500	125	125	375
Neck (thyroid)	15,000	3,750	375	937

* No maximal permissible limits are set for patient exposure.
ALARA = as low as reasonably achievable; MPD = maximal permissible dose.

hospital radionuclide and x-ray personnel show that the mean annual dose for 1975 was 350 mrem (3.5 mSv); 90% of all personnel, including angiographers, had cumulative annual doses of less than 500 mrem (5 mSv).[11] Average exposures for different types of cardiac catheterization procedures are shown in Table IV.[6]

Equipment Considerations

Cineradiographic exposure depends on the radiation dose per frame and the length of the filming time. Published x-ray exposures range from 10 to 120 μR/frame.[23] At the usual rate of 60 frames/s and 25 μR/frame, the adult skin exposure rate ranges from 45 to 90 R/min (0.45 to 0.9 Sv/min). A lesser radiation dose per frame would produce a poor-quality image due to statistical fluctuations in the spacial distribution of x-ray photons on the film (quantum mottle). The report of the Inter-Society Commission for Heart Disease Resources[24] has recommended 30 to 40 μR/frame for a 15- to 17-cm field-size image intensifier as a balance between picture quality and minimal radiation exposure to the patient. Included in this report[24] are recommendations for beam limitation devices, reduction of scatter by additional shielding around the table, and other shields to protect personnel not required in the room for performance of the procedure. A cardiologist should be aware of the output of the x-ray equipment being used. For example, the microroentgen per frame measurements should be made annually or each time a major component of the x-ray unit is changed. A comprehensive quality control program should be implemented to optimize the performance of other components in the cineradiographic system, such as x-ray generators, image intensifiers, optical systems and film processors.[23]

Protective Measures: Time, Distance and Shielding

Specific radiation protection measures that are applicable to all cardiac catheterization laboratories are difficult to prescribe. Certain general radiation protection principles can be adapted for each laboratory. Three variables are the duration of the radiation, shielding and the distance of personnel from the x-ray source.

TABLE IV Average Calculated Time and Exposure for Eye and Thyroid During Cardiac Catheterization*

	Time (min)	Exposure mrem (mSv)	
		Eye	Thyroid
Right heart catheterization	15.3	4.9 (0.049)	4.2 (0.042)
Left ventriculography	9.4	3.3 (0.033)	2.8 (0.028)
Right coronary angiography	10.5	9.1 (0.091)	7.7 (0.077)
Left coronary angiography	7.0	6.5 (0.065)	6.2 (0.062)
Total procedure	50.4	31.1 (0.311)	27.6 (0.276)

* Modified from Rueter.[6]

About half of the cardiac catheterization exposure comes during fluoroscopy and the remainder during cineangiography.[4,6,10] The fluoroscopy time can be considerably reduced by using short bursts on the fluoroscope rather than a prolonged, continuous exposure.

The limiting occupational exposure to physicians performing cardiac catheterization is eye exposure. Rueter[6] estimated that the lens of the eye of the cardiologist receives an average exposure of 20 mR (0.2 mSv) during coronary angiography, left ventriculography and related fluoroscopy.[6] Figures 1 and 2 show the intensity and distribution of scattered radiation around the angiography table. Based on a recommended maximal dose of 100 mrem (1 mSv)/week to the lens of the eye for occupational workers, a cardiologist should be limited to approximately 5 procedures per week. Rotation of nurses and technicians into nonradiologic areas increases the time interval between exposures and may lessen the likelihood of an individual receiving an excessive exposure.

Newer angiographic equipment with U-arms or C-arms allows compound angled oblique projections. Because the x-ray beam must penetrate an additional thickness of tissue with this equipment, the 40° cranial view may have 2 to 3 times the entrance dose of a stan-

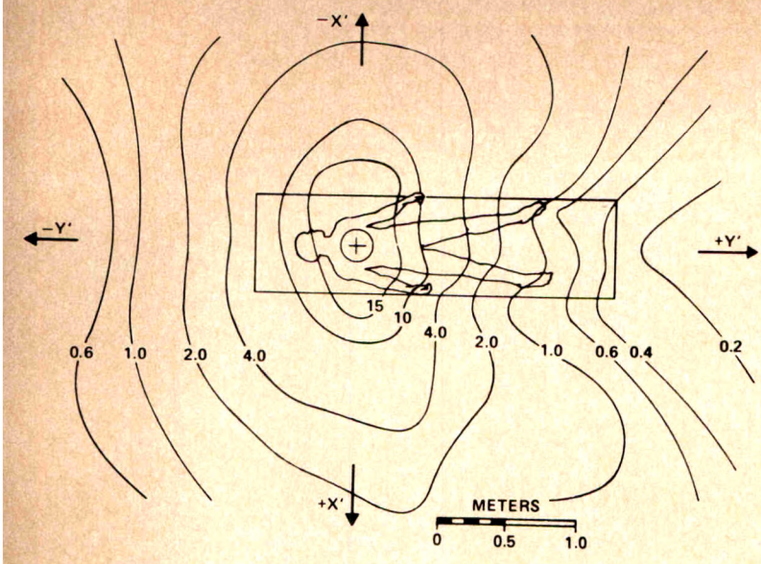

FIGURE 2. Pattern in the horizontal plane of exposure values (milliroentgen/hour) during cardiac catheterization. Typical values of 96 kVp, 10 × 10 cm field and 1.95 R/min tabletop exposure rates were used. (Reprinted by permission of the American Heart Association and from Rueter.[6])

dard frontal projection.[25] The cranial position of the x-ray tube during angulation can result in more scattered radiation to medical personnel (Fig. 3).

The concern about x-ray exposure during pregnancy has been discussed both for the woman as a patient and for the physician performing the catheterization. The American College of Obstetricians and Gynecologists in their guidelines for diagnostic x-ray examinations have suggested that attempts to schedule studies of women of reproductive age in relation to menstrual cycle are of little value, and there is no measurable advantage for scheduling examinations at any particular time during the normal menstrual cycle.[26] An estimation of a conceptus dose in pregnant woman radiologists has suggested that a woman cardiologist would receive less than 1 mrem (0.01 mSv) of gonadal dose per examination and therefore could perform 5 catheterizations per day and still receive less than the maximal permissible conceptus dose of 500 mrem (5 mSv)/gestation.[27]

Because radiation decreases as the square of the distance from the source, all personnel who are not needed in the room should be located elsewhere. For instance, the electrophysiologic data collection can be performed from a remote location rather than beside the fluoroscopy table. Nurses and technicians who remain in the room should be as far away as practical from the x-ray tube. Although coronary angiography is traditionally performed by using a hand-injection technique, all angiographic procedures can be accomplished with a power injector, thereby allowing all personnel to leave the room during the cineangiography.

Lead shielding is the third method to reduce personnel exposure. Collimation of the x-ray beam reduces secondary scatter to the patient and physician and also improves image quality. Movable shields or drapes are available for most of the current angiographic units. Side drapes between the patient and operator reduce scatter from the patient that would otherwise be received by the cardiologist. Specially designed shields have been developed for C-arm imaging systems, which are used for compound hemiaxial projections.[28] Because the thyroid and eyes receive most of the scattered radiation, thyroid shields and leaded eyeglasses may be used by a full-time angiographer.[29] These protective devices are recommended by the ALARA guidelines for those who perform many studies. Multilayered lead aprons with the equivalent of 0.5 mm of lead are available in multiple configurations. The selection of an apron will depend on the task of the laboratory personnel; technologists with their back to the patient should wear a full wraparound apron. If this type of apron is too heavy, a 2-piece apron is available consisting of a jacket and a skirt.

Protection of the patient during cardiac catheterization consists mainly of shielding the gonadal area. Once the catheters have been introduced from a femoral arterial site, both male and female patients should have the reproductive organ dose decreased by placing a lead apron beneath the pelvis for an under table tube location. Gonadal shielding is of particular importance in pediatric patients because the primary beam centered on the thorax is much closer to the gonads than in the adult.

Conclusion

There is no dose of radiation that can be considered safe or harmless. Because diagnostic x-rays are the greatest single source of man-made radiation, the physician must assess judiciously the benefits and risks of medical x-rays. Exposure of patients with almost certain pathologic findings to x-ray radiation is justified to produce a diagnostic image if danger of the present disease outweighs the small probability of future hazard from radiation. Examples are the patient who is to undergo coronary artery surgery or the cyanotic infant who needs an immediate and accurate anatomic diagnosis. However, in a longer time frame, the physician, nurses and technologists working in the cardiac catheterization laboratory are subjected to a very low dose of scattered radiation, which is absorbed over a period of months to years to decades. Personnel dose-reduction techniques

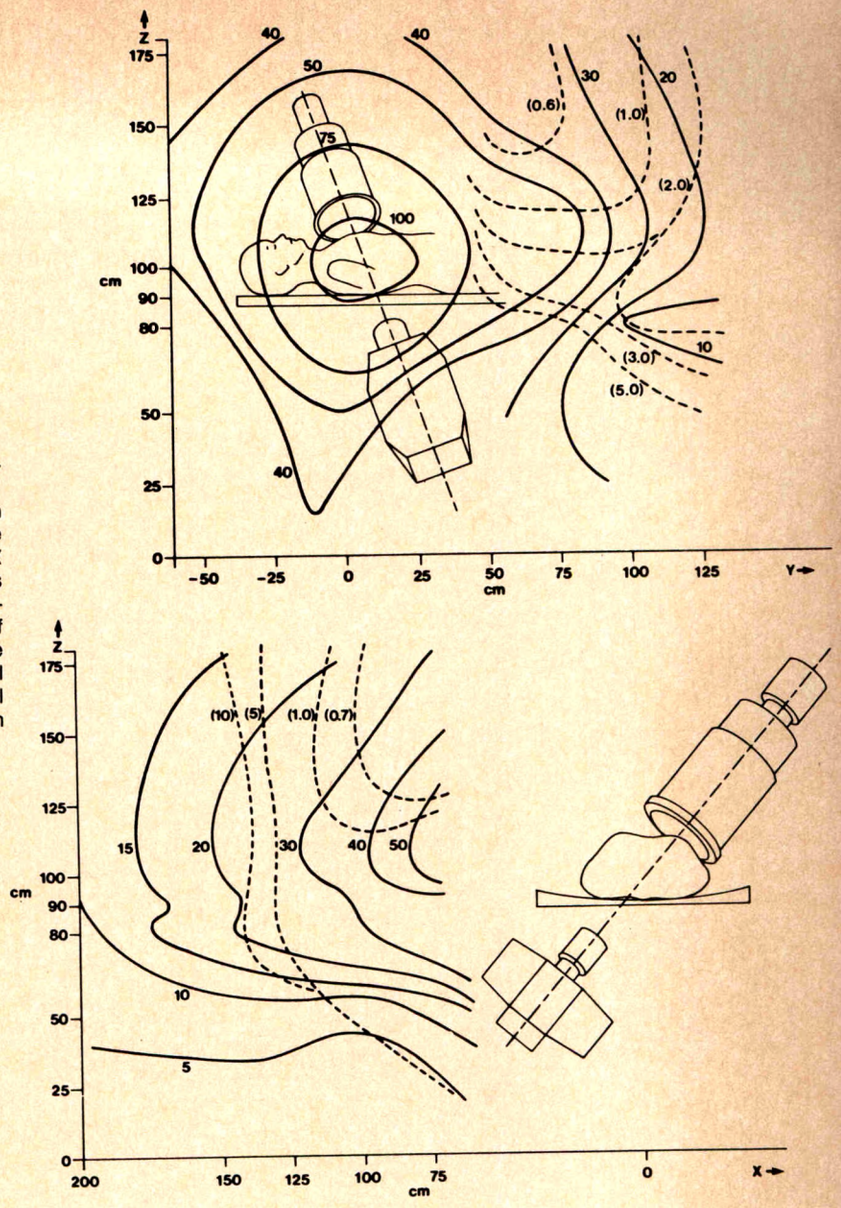

FIGURE 3. Isoexposure curves expressed in milliroentgen/hour for the 50° left anterior oblique 15° cranial angulation in (top) the longitudinal plane with the operator at 75 cm on the Y axis, and (bottom) the horizontal plane with the operator at 75 cm on the X axis. **Solid lines** indicate radiation exposure levels without the protection of the shield; **dashed lines** indicate values with the shield. The vertical center of shield is at 75 cm in both the X and Y planes with the operator behind the shield. Z represents the vertical plane, Y the longitudinal plane, and X the horizontal plane. (Reprinted by permission of publisher from Gertz et al.[28])

should consider the time of the study, placement of personnel, available shielding, location of equipment, adequate monitoring (radiation badge) and a complete quality control program. The aim of an adequate radiation protection program is to reduce the genetic and somatic risks to below the risk for other occupations regarded as safe.[30,31] Risk estimates in the low-dose region involve a great deal of uncertainty and are based in part on incomplete data. The magnitude of the risk to the persons exposed must be kept in perspective if they are to derive a benefit from the medical use of ionizing radiation.

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Accuracy of Left Ventricular Ejection Fraction Using the Nuclear Stethoscope in Left Ventricular Aneurysm

DAVID M. McCARTHY, MD, and P. TODD MAKLER, Jr., MD

Although the nuclear stethoscope, a nonimaging probe, accurately determines left ventricular (LV) ejection fraction (EF), its reliability in patients with LV aneurysm has not been established. Accordingly, LVEF was determined using the nuclear stethoscope and compared with that determined by equilibrium gated blood pool scanning in 29 patients, 1 studied on 2 separate occasions, for a total of 30 patient studies. Patient studies were separated into 2 groups. Patients in group I (n = 20) had no gated blood pool evidence for aneurysm, and those in group II (n = 10) had discrete focal akinesia or dyskinesia. Nineteen patients (13 in group I and 6 in group II) had 2 separate nuclear stethoscope acquisitions. In group I, EF determined by gated blood pool scanning (53 ± 4%, mean ± standard error) did not differ from that determined by nuclear stethoscope (51 ± 4%). EF determined using either gated blood pool scanning (32 ± 6%) or nuclear stethoscope (35 ± 5%) was significantly lower in group II than in group I, although nuclear stethoscope and gated blood pool scanning did not differ. Reproducibility was excellent (r = 0.96). Overall, nuclear stethoscope and gated blood pool EFs correlated closely (r = 0.93), and the correlation coefficients were similar in groups I (r = 0.92) and II (r = 0.92). The slopes of the regression curves for group I (0.97) and group II (0.92) were not statistically different. These results confirm the accuracy and reproducibility of LVEF determination by nuclear stethoscope and specifically demonstrate its reliability in patients with LV aneurysm.

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Nonimaging nuclear probes accurately determine left ventricular (LV) ejection fraction (EF).[1–7] These devices consist of a single-crystal and photomultiplier tube. They are portable and significantly less complex and expensive than standard nuclear medicine camera-computer imaging systems. The counting rate sensitivity also permits measurement of LV function on a beat-to-beat basis.[5,8] This probe has 2 attributes that may limit its usefulness in patients with LV aneurysm: A fixed region-of-interest is used for data acquisition and analysis, and the instrument is positioned "blindly" over the heart. These potentially limiting effects in patients with LV aneurysm have been discussed,[5] and decreased accuracy of EF determination in such patients has been reported.[6] Because global LVEF has important prognostic and therapeutic implications,[9,10] the reliability of such determination in patients with LV asynergy is important. This study evaluates the accuracy of LVEF by a nonimaging probe in patients with and without LV aneurysm.

From the Departments of Medicine (Cardiovascular Section) and Radiology (Nuclear Medicine), University of Pennsylvania School of Medicine, and the Nuclear Cardiology Laboratory, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. Manuscript received June 11, 1984; revised manuscript received August 24, 1984, accepted August 27, 1984.

Address for reprints: David M. McCarthy, MD, Cardiovascular Section, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

Methods

Patients: The patient population comprised 29 patients undergoing routine gated blood pool (GBP) scanning for clinical indications. There were 20 men and 9 women, aged 32 to 84 years (mean 55). One patient was studied on 2 separate occasions, for a total of 30 patient studies. The patients were separated into 2 groups based on the results of the GBP scanning. Group I comprised 19 patients (1 studied twice for a total of 20 studies) with no evidence of LV aneurysm. LV wall motion was normal in 14 and hypokinetic in 5. Cardiac diagnoses included coronary artery disease in 4 patients, congestive heart failure in 4, valvular heart disease in 3, hypertensive heart disease in 3, and hypertrophic cardiomyopathy in 1 patient; 4 patients had no heart disease. Group II comprised 10 patients with coronary artery disease (1 with coexisting valvular heart disease and 8 with ventricular tachycardia) who had discrete akinesia or dyskinesia indicative of LV aneurysm.[11] Dyskinesia was present in 5 patients and akinesia in 5. The location of the aneurysm was inferior in 2 patients, inferoapical in 2 and apical in 6. Confirmation of the presence of LV aneurysm was available by 2-dimen-

sional echocardiography (2 patients) or cardiac catheterization (8 patients, 4 of whom also had surgical confirmation).

Study design: Patients were included in the study if the nonimaging probe study could be performed at the time of GBP scanning. Red blood cells were labeled in vivo using 15 mCi of technetium-99m pertechnetate.[12] LVEF was determined in all patients by both a standard GBP camera technique and a nuclear probe. The sequence of studies alternated (i.e., GBP or probe study first). The results of the first EF determination were not made available to the person making the second determination.

Nuclear stethoscope: Probe studies were performed on a commercially available computerized nuclear probe, the Nuclear Stethoscope® (Bios, Inc.), which consists of a 2-inch-diameter × 1½-inch-thick NaI (Tl) crystal with a single-bore 3.5 inch converging collimator which is interfaced to a dedicated microprocessor. This instrument has been described in detail elsewhere.[13] The probe was positioned over the heart using a previously described computer-assisted algorithm.[5] Once the probe was positioned, gated equilibrium studies were initiated in the ventricular function mode for 60 or 120 seconds, depending on the observed count rate. Typical count rates in this study were 1,500 counts/50 ms (i.e., 30,000 counts/s). In 19 patients, 2 separate probe studies were performed with complete repositioning of the instrument between studies. All probe studies were performed by 1 of 2 physician operators who had previous experience with the nuclear stethoscope.

Gamma camera studies: Multigated blood pool imaging was performed on a single-crystal gamma camera (Picker-Dynamo®) interfaced to a dedicated nuclear medicine minicomputer (DEC Gamma-11®). Studies were acquired in the anterior, "best septal" (usually 35 to 45°) left anterior oblique (LAO), and 70° LAO views. R-wave synchronized multigated scans were acquired with 24 frames spanning the cardiac cycle for an average of 250,000 counts/frame. Beats that fell outside a ±10% RR interval window were rejected. LVEF was calculated from the "best septal" LAO view using a variable region-of-interest software program. The calculation was performed by an independent observer who was not aware of the results of nuclear stethoscope studies. Wall motion was assessed in all 3 views for the presence or absence of LV aneurysm (discrete akinesia or dyskinesia).[11]

Statistical analysis: Data are expressed as the mean ± standard error of the mean (SEM). Differences were analyzed using a Student *t* test for paired or unpaired data as appropriate. The EF determinations by gamma camera and nuclear stethoscope were compared using linear regression analysis, as was the reproducibility of nuclear stethoscope determination in the 19 patients undergoing 2 determinations. The slopes of the regression lines for patients with and without aneurysm were compared using the 2-tailed Student *t* test.[14]

Results

Among the 30 determinations in the 29 patients, EFs ranged from 11 to 82%. The mean GBP EF in group I was 53 ± 4%, which was not significantly different from the nuclear stethoscope EF (51 ± 4%) (Fig. 1). In group II, the GBP EF was 32 ± 6%, which was significantly less than that in group I ($p < 0.05$). Again, the nuclear stethoscope EF (35 ± 5%) did not differ significantly from that determined by GBP scanning.

In the entire group, linear regression analysis revealed a close relation ($r = 0.93$) between EF calculated by either nuclear stethoscope or GBP scanning: $EF_{NS} = 0.92\ EF_{GBP} + 0.04$. When the 2 groups were analyzed individually, this close correlation between the 2 techniques remained. In group I (Fig. 2), the EF determinations were closely correlated ($EF_{NS} = 0.97\ EF_{GBP} + 0.01$, SEE = 0.08, $r = 0.92$). In group II (Fig. 3), $EF_{NS} = 0.92\ EF_{GBP} + 0.06$, SEE = 0.07, $r = 0.92$. In the 19 patients who had 2 separate nuclear stethoscope determinations (13 from group I and 6 from group II), reproducibility was excellent (Fig. 4): $y = 0.96x + 0.02$, SEE = 0.05, $r = 0.96$.

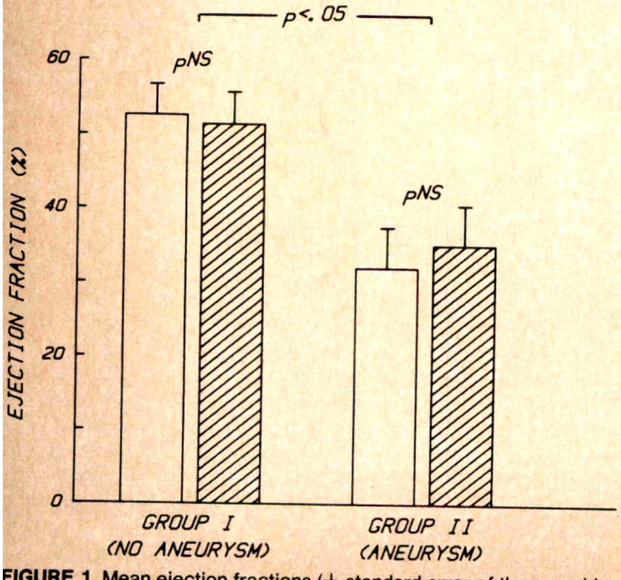

FIGURE 1. Mean ejection fractions (± standard error of the mean) by gated blood pool scanning (**open bars**) and nuclear stethoscope (**hatched bars**). NS = not significant.

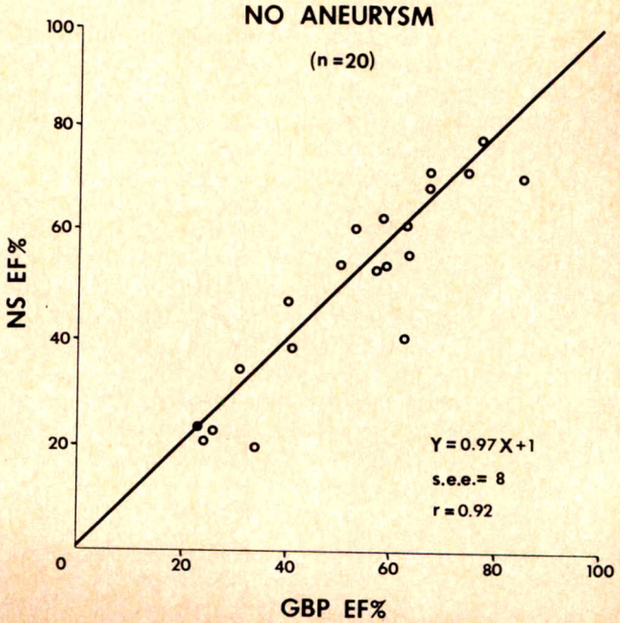

FIGURE 2. Comparison of ejection fraction (EF %) by nuclear stethoscope (NS) and gated blood pool (GBP) scanning in group I.

Discussion

The results of this study confirm the accuracy of LVEF determination using the nuclear stethoscope, and in particular demonstrate its accuracy in patients with LV aneurysm. Previous studies using the nuclear stethoscope[4–7] or other nonimaging probes[1–3] have also demonstrated the accuracy of LVEF determination by this method. Wagner et al[4] evaluated 2 versions of the nuclear stethoscope. A prototype model yielded a good correlation with camera-computer EF determination (r = 0.81), and improved with a later version similar to the present instrument in which positioning is facilitated by a microprocessor-based algorithm (r = 0.92). These studies were conducted on a series of patients, some of whom had coronary artery disease, but without comment on the presence or absence of regional wall motion abnormalities. Other investigators, using either the nuclear stethoscope[5–7] or other nonimaging probe devices[1–3] have reported correlation coefficients vs standard (radionuclide or catheterization) techniques ranging between 0.85 and 0.92.

The nuclear stethoscope is a nonimaging radionuclide detector that differs from standard camera-computer studies in several respects, at least 2 of which may limit its accuracy in patients with LV aneurysm. First, the device is positioned "blindly" over the left ventricle. Positioning has been facilitated by the use of a microprocessor-based algorithm which monitors relative stroke count changes on a beat-to-beat basis as the probe is moved in position over the chest.[5,13] Although this positioning algorithm has improved the accuracy of LVEF determination,[4] it could lead to an overestimation of true EF in patients with aneurysm if the probe is positioned over a normally contracting region and excludes the area of akinesia or dyskinesia. Also, since the probe uses a fixed region of interest to assess changes in LV volume, an enlarged left ventricle may be incompletely viewed by the device, resulting in an underestimation of the true EF.

These and other technical limitations of nuclear probes have been discussed,[3,5] and the results of EF determination in patients with dyssynergy have been inconsistent. Berger et al[5] studied 71 randomly selected patients, including 23 with discrete regional wall motion abnormalities. Their overall correlation with radionuclide EF was good (r = 0.92), and they reported that the correlation between probe and camera EFs was comparable in patients with and without regional wall motion abnormalities. However, Strashun et al[6] compared the nuclear stethoscope EF in 42 patients with normal wall motion and in 26 patients with regional asynergy, and found a better EF correlation in the group with uniform wall motion (r = 0.86) than in the group with regional abnormalities (r = 0.68). In the latter group, there was a significant overestimation of EF by the nuclear stethoscope. In the study of Høilund-Carlsen et al,[7] the EF determined by nuclear stethoscope in 12 patients with wall motion abnormalities was significantly higher than that measured by gamma camera, while the EFs in patients with normal contraction patterns were slightly (but insignificantly) less than those measured by gamma camera. Correlation coefficients for each subgroup were not reported. Bacharach et al[3] reported a good correlation coefficient (r = 0.90), even though 11 of their 20 patients with coronary artery disease had wall motion abnormalities.

In the present study, patients were grouped according to the presence or absence of LV aneurysm. Although

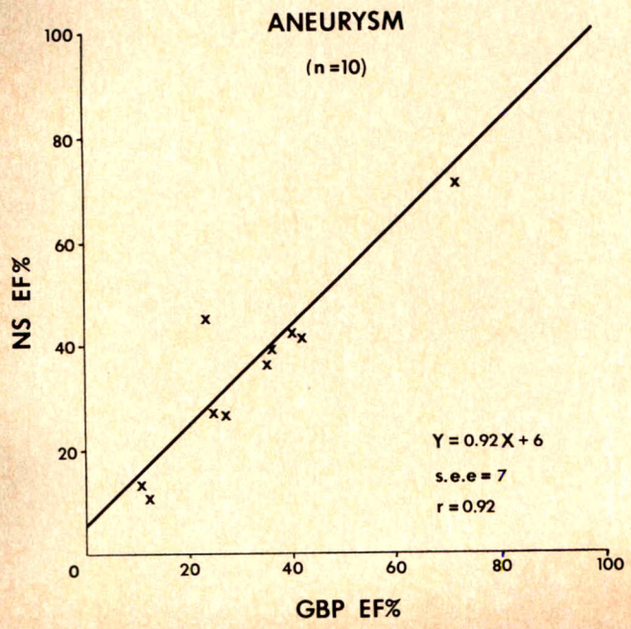

FIGURE 3. Comparison of ejection fraction (EF%) by nuclear stethoscope (NS) and gated blood pool (GBP) scanning in group II.

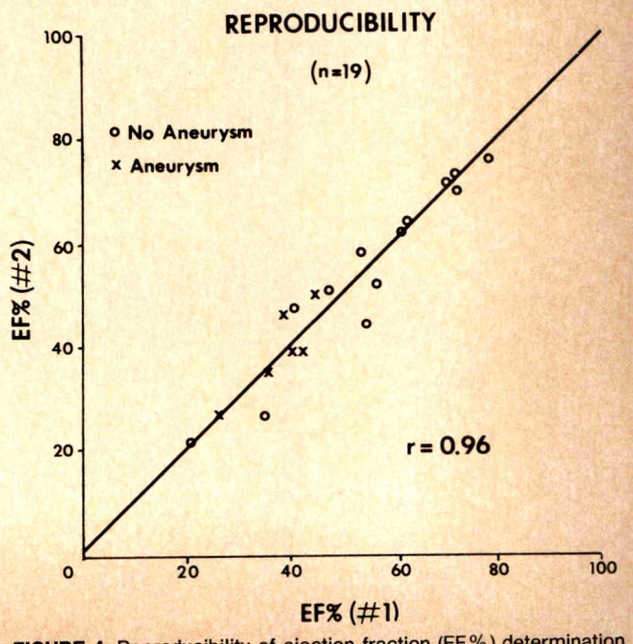

FIGURE 4. Reproducibility of ejection fraction (EF%) determination using the nuclear stethoscope with 2 separate data collections.

the mean LVEF by nuclear stethoscope (35 ± 5%) was slightly higher than that by gamma camera (32 ± 6%) in the patients with aneurysm, this difference was not statistically significant. In addition, the correlation coefficients and standard errors of the estimate of EF determination in the group with aneurysm was similar to that in the group without aneurysm (Fig. 2 and 3). The slope of the regression line in the patients with aneurysm (0.92) was not statistically different from that in the patients without aneurysm (0.97). Reproducibility was excellent for both types of patients (Fig. 4).

Berger et al[5] discussed the theoretical overestimation of true EF in aneurysm patients and stated that it may apply mostly to patients with inferior dyssynergy, rather than the more common anteroapical aneurysms. The differential effects of regional abnormalities of LV function on a global EF determination have been shown in phantom studies.[15] In the present study, 2 patients had inferior aneurysms and 2 had inferoapical aneurysms; thus, the theoretical limitation may have been masked by the presence of 6 patients with anterior aneurysms. It is also possible that the theoretical overestimation (due to exclusion of the dyskinetic region from the field of view) is balanced by the theoretical underestimation in patients with LV dilatation.[5] Most patients with aneurysm in the present study had evidence of LV dilatation as well as regional akinesia or dyskinesia.

Acknowledgment: We thank Charles Colvin for technical assistance and Geri McCausland for preparation of the manuscript.

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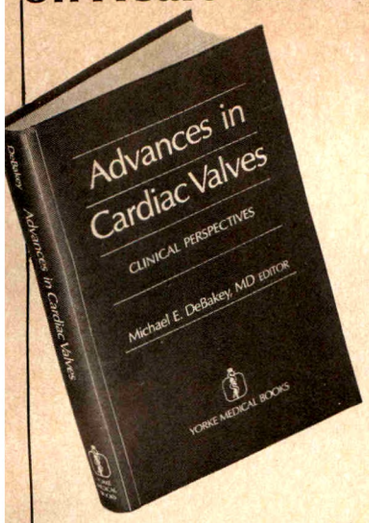

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CONTRIBUTORS INCLUDE

Mauro Abbate
Franz W. Amann
Manuel J. Antunes
Kit V. Arom
P. Barzellotti
Enrico Baruffi
Giuseppe Battaglia
Eugene M. Baudet
Marco Benedetti
Dieter Burckhardt
Jorge L. Camunas
R. Carlier
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Complete blood counts, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms.

A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Use MAO inhibitors with caution in patients receiving hydralazine.

When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and Apresoline (hydralazine hydrochloride) are used concomitantly.

Usage in Pregnancy

Animal studies indicate that hydralazine is teratogenic in mice, possibly in rabbits, and not in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should not be used during pregnancy unless the expected benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Myocardial stimulation produced by Apresoline can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The "hyperdynamic" circulation caused by Apresoline may accentuate specific cardiovascular inadequacies. An example is that Apresoline may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from Apresoline, but is less common than with ganglionic blocking agents. Use with caution in patients with cerebral vascular accidents.

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lood dyscrasias, consisting of reduction in hemoobin and red cell count, leukopenia, agranulocyosis, and purpura, have been reported. If such bnormalities develop, discontinue therapy. Periodic lood counts are advised during prolonged therapy.

he Apresoline tablets (10 and 100 mg) contain D&C Yellow No. 5 (tartrazine) which may cause llergic-type reactions (including bronchial asthma) n certain susceptible individuals. Although the overll incidence of FD&C Yellow No. 5 (tartrazine) ensitivity in the general population is low, it is requently seen in patients who also have aspirin ypersensitivity.

ADVERSE REACTIONS

Adverse reactions with Apresoline are usually reversble when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.

Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris.

Less frequent: Nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE AND ADMINISTRATION

Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective levels.

The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.

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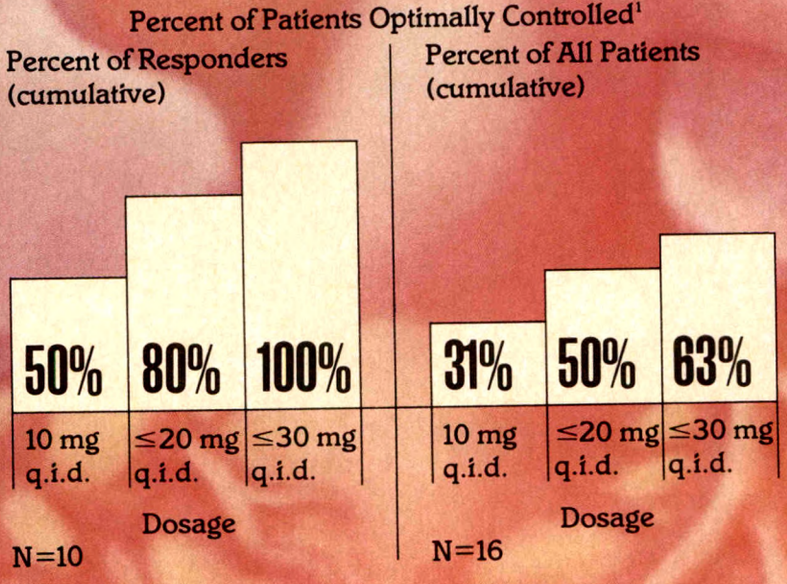

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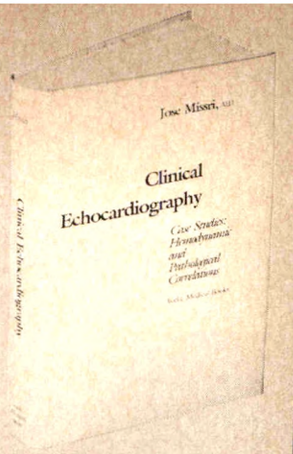

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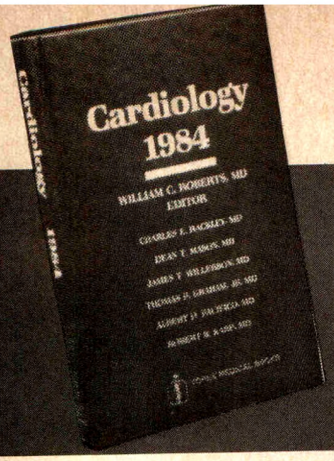

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Charles E. Rackley, MD
Chairman, Department of Medicine Anton and Margaret Fuisz Professor of Medicine Georgetown University Medical Center Washington, D.C.

Dean T. Mason, MD
Physician-in-Chief Western Heart Institute St. Mary's Hospital and Medical Center San Francisco, California Editor-in-Chief, American Heart Journal

James T. Willerson, MD
Professor of Medicine Chief, Division of Cardiology Department of Medicine University of Texas Health Science Center Dallas, Texas

Thomas P. Graham, Jr, MD
Professor of Pediatrics Chief, Division of Pediatric Cardiology Department of Pediatrics Vanderbilt University Nashville, Tennessee

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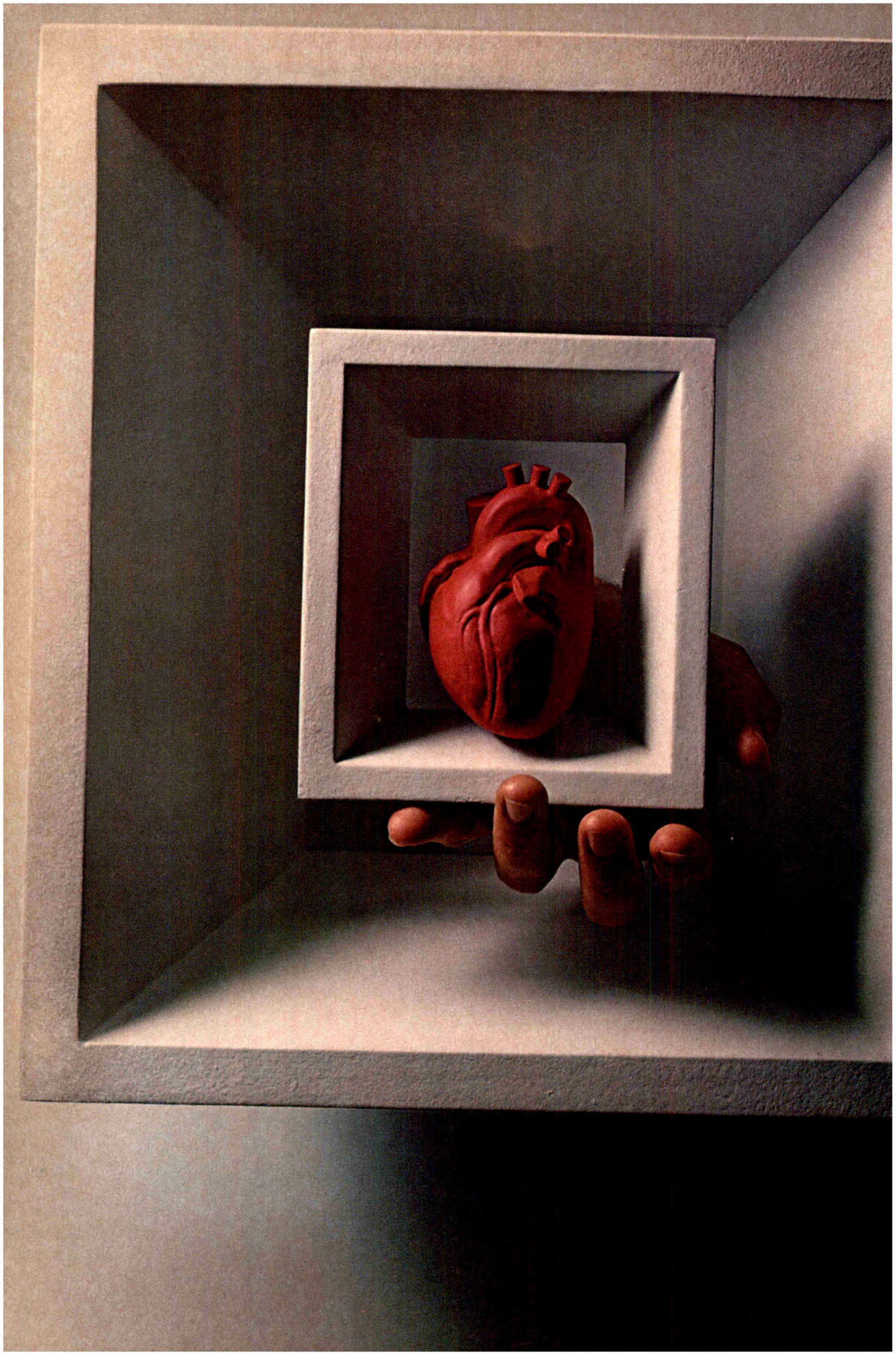

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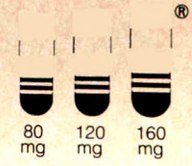

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the platelets of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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Association of Methemoglobinemia and Intravenous Nitroglycerin Administration

KERRY J. KAPLAN, MD, MARK TABER, MD, J. RUSSELL TEAGARDEN, RPh, MICHELE PARKER, RN, MS, and RICHARD DAVISON, MD

Significant elevation of arterial methemoglobin levels has been reported with the administration of intravenous (i.v.) nitroglycerin (NTG). To determine the incidence and clinical significance of this side effect of i.v. NTG, serial arterial methemoglobin levels were determined in 50 consecutive patients receiving i.v. NTG for 48 hours or longer. The mean i.v. NTG infusion rate was 290 ± 13 μg/min (4.1 ± 0.2 μg/kg/min) and the mean duration of infusion was 7.1 ± 0.5 days. The mean methemoglobin level for the 141 samples was 1.57 ± 0.08%, which differs from the control mean value in our laboratory of 0.44 ± 0.01%. Although no patient had clinical symptoms from methemoglobin, 20 patients had elevated (>1%) levels on at least 1 measurement. Seventy-eight of the 141 samples analyzed were in the normal range; 63 determinations were between 2 and 5%. Patients with normal methemoglobin levels differed from those with abnormal levels in the dose of i.v. NTG (mean infusion rate 244 ± 16 vs 351 ± 17 μg/min; total cumulative dose 1,612 ± 153 vs 3,398 ± 308 mg). Age, weight, renal and hepatic function, and arterial oxygen saturation were not different between the groups. In conclusion, clinically significant methemoglobinemia is uncommon with i.v. NTG infusion; however, when large doses of NTG are administered, this complication is more likely. (Am J Cardiol 1985;55:181–183)

Clinically significant methemoglobinemia during the administration of organic nitrates, including intravenous (i.v.) nitroglycerin (NTG), has been reported recently.[1–3] This oxidized (ferric) form of hemoglobin cannot bind or release oxygen and causes a leftward shift in the oxyhemoglobin dissociation curve.[4,5] We undertook a prospective study to determine the frequency and clinical significance of methemoglobinemia in patients treated with i.v. NTG.

Methods

Serial methemoglobin levels were measured in 50 consecutive patients treated with i.v. NTG for at least 48 hours. NTG in concentrations of either 300 or 600 μg/ml was infused through either polyvinyl chloride or polyethylene-polypropylene tubing. The infusion rate was controlled by an IMED volumetric infusion pump. The infusion rate was started at 25 to 50 μg/min and increased as tolerated at 25- to 50-μg/min increments to control angina pectoris.[6] Topical, oral and sublingual nitrates were administered as ordered by the attending physician.

Arterial blood samples were obtained 48 to 72 hours after NTG administration was initiated and repeated at 24- to 72-hour intervals during the duration of the infusion. Samples were collected in heparinized syringes and placed on ice for immediate transport to the blood gas laboratory, where they were analyzed on an IL 282 cooximeter for methemoglobin, expressed as percent (to the nearest whole number) of total hemoglobin present in the oxidized or methemoglobin state.

Results are expressed as mean ± standard error of the mean. Standard t tests were used to compare groups.

Results

The 50 patients in the study group included 26 men and 24 women, average age 63.6 ± 1.4 years. The indication for i.v. NTG was unstable angina in 11 patients (22%) and angina after myocardial infarction in 39 patients (78%). Intravenous NTG was administered continuously for a mean of 7.1 ± 0.5 days (range 1 to 30). The mean i.v. NTG infusion rate was 290 ± 13 μg/min (range 30 to 1,000) or 4.1 ± 0.2 μg/kg/min (range 0.4 to 12.6). In addition, 43 patients were receiving NTG ointment at a mean daily dosage of 18.0 ± 1.6 inches and 33 patients were receiving isosorbide dinitrate in a mean total oral dose of 299 ± 40 mg/day.

From the Section of Cardiology, Department of Medicine, Northwestern University Medical School, and the Departments of Nursing and Pharmacy, Northwestern Memorial Hospital, Chicago, Illinois. Manuscript received April 26, 1984; revised manuscript received August 31, 1984, accepted September 4, 1984.

Address for reprints: Kerry Kaplan, MD, Wesley—628, 251 East Chicago Avenue, Chicago, Illinois 60611.

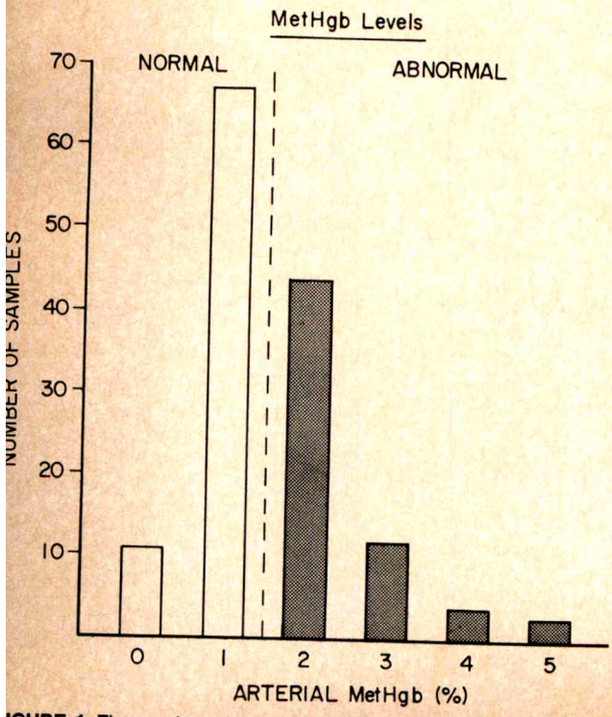
TABLE I Patient Characteristics

	Methemoglobin (0–1%) (n = 78)	Methemoglobin (2–5%) (n = 63)	p Value
Age (yr)	64 ± 1	65 ± 1	NS
Weight (kg)	76 ± 2	73 ± 1	NS
Creatinine (mg/dl)	1.2 ± 0.1	1.4 ± 0.1	<0.08
Blood urea nitrogen (mg/dl)	19 ± 0.9	20 ± 1.5	NS
Alk phos (mU/ml)	96 ± 3	105 ± 8	NS
Total bilirubin (mg/dl)	0.6 ± 0.04	0.4 ± 0.04	NS
PaO_2 (Torr)	74 ± 2	77 ± 2	NS
O_2 saturation (%)	94 ± 1	93 ± 1	NS

Alk phos = alkaline phosphatase; NS = not significant; PaO_2 = oxygen partial pressure.

A total of 141 arterial samples were analyzed for methemoglobin. The mean methemoglobin level for these samples was 1.57 ± 0.08%, which is higher than the mean normal value for our laboratory, 0.44 ± 0.01%.[7] Abnormal methemoglobin levels are defined as more than 1%, which is the mean plus 2 standard deviations. Twenty patients had abnormal methemoglobin levels on at least 1 determination, but in no instance could clinical manifestations be attributed to this finding. Methemoglobin levels ranged from 0 to 5% of total hemoglobin (Fig. 1). Seventy-eight of the 141 samples were 0 or 1% and 63 determinations were between 2 and 5%.

In an attempt to identify the factors involved in the development of elevated methemoglobin, all blood samples were classified as having normal (≤1%) or abnormal (>1%) methemoglobin levels. The patients



IGURE 1. The number of samples for each arterial methemoglobin MetHgb) level. The samples are divided into normal (0 to 1%) and bnormal (2 to 5%) values.

TABLE II Nitrate Therapy

	Methemoglobin (0–1%)	Methemoglobin (2–5%)	p Value
IV NTG μg/min	244 ± 16	351 ± 17	<0.001
μg/kg/min	3.2 ± 0.2	5.0 ± 0.3	<0.001
days	5.1 ± 0.3	9.7 ± 1.0	<0.001
mg (cumulative dose)	1,612 ± 153	3,398 ± 308	<0.001
NTG ointment (inches/day)	17 ± 1	20 ± 1	NS
Isosorbide dinitrate (mg/day)	295 ± 24	305 ± 33	NS

NS = not significant; NTG = nitroglycerin.

whose samples had normal methemoglobin levels were compared with those whose samples had abnormal methemoglobin levels. Age, weight, renal and hepatic function tests, and arterial oxygen saturation were not significantly different between the 2 groups (Table I). However, the i.v. NTG therapy at the time of sampling was different between the groups (Table II). The mean i.v. NTG infusion rate in patients with a normal methemoglobin level was 244 ± 16 μg/min, and that in patients with an elevated methemoglobin level was 351 ± 17 μg/min. The dose expressed in μg/kg/min was also significantly different. The duration of the i.v. NTG infusion was significantly longer in patients with abnormal methemoglobin levels, 9.7 ± 1.0 vs 5.1 ± 0.3 days. Predictably, the patients with elevated methemoglobin levels had a significantly greater total cumulative i.v. NTG dose (3,398 ± 308 mg) than those with normal levels (1,612 ± 153 mg). When the doses of NTG ointment or isosorbide dinitrate are compared, there is no significant difference between groups.

As the total cumulative dose of i.v. NTG increases, so does the percentage of samples with abnormal methemoglobin values (Fig. 2). For purposes of reference, a patient receiving a continuous infusion of 300 μg/min of NTG would receive approximately 450 mg/day.

After completion of the data collection for this study, a patient receiving i.v. NTG was found, in a routine arterial blood sample, to have a methemoglobin level of 12%. No clinical manifestations could be attributed to this finding. After tapering of the i.v. NTG dose, the arterial methemoglobin level rapidly returned to 0. A determination of the major methemoglobin-reducing enzyme, NADH ferricyanide reductase,*[8] revealed it to be in the normal range (patient 21.4, control 15.3, normal 19.2 ± 3.8), thus excluding the possibility of a congenital enzyme deficiency. The elevated methemoglobin level in this patient may have been the result of the simultaneous administration of i.v. NTG and phenazopyridine (Pyridium®), which is an aniline dye whose use has been associated with methemoglobinemia.[9]

Discussion

Methemoglobinemia interferes with oxygen delivery in 2 ways: (1) In the oxidized form, hemoglobin cannot release or take up oxygen,[4] and (2) its presence shifts the oxyhemoglobin dissociation curve to the left.[5] A bluish

* NADH ferricyanide reductase assays were kindly performed by Dr. E. Beutler, Scripps Institute, La Jolla, California.

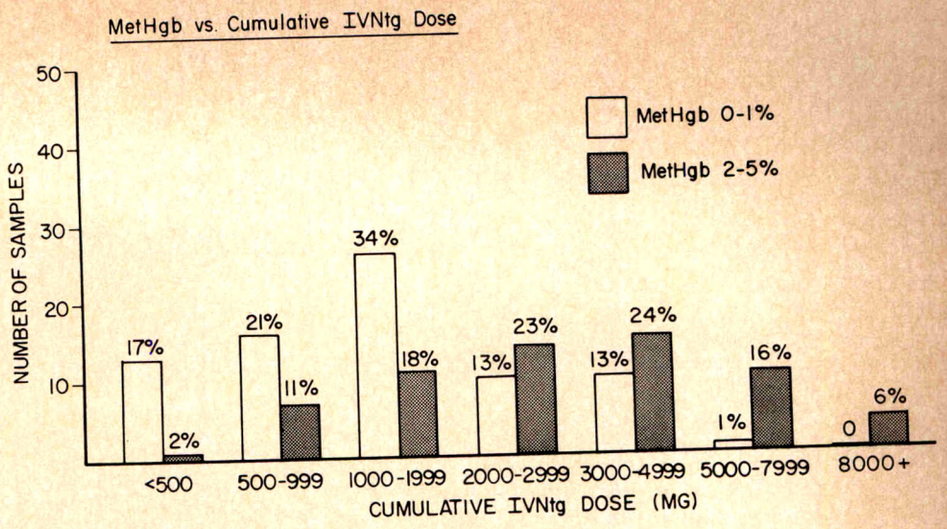


FIGURE 2. A comparison of total, cumulative dose of intravenous nitroglycerin (IVNtg) received and number of normal vs abnormal methemoglobin (MetHgb) samples. A modified logarithmic scale is used for cumulative IV NTG dose in order to make the number of samples in each range comparable. The **numbers above the bars** refer to the percentage of all normal or abnormal samples in that range of doses.

discoloration of the skin occurs at total methemoglobin levels of 1.5 g. When 30% of hemoglobin is present as methemoglobin, mild fatigue, lethargy, headache and a decrease in exercise tolerance occur. When methemoglobin levels reach 60%, symptoms of inadequate tissue oxygenation occur such as dyspnea, coma or convulsions. The lethal level of methemoglobin in humans is above 70%.[10] However, the additive effects of coexistent anemia, hypoxemia and decreased cardiac output must also be considered and in these circumstances patients could become symptomatic at lower levels.

The metabolism of NTG occurs both in the liver and at various peripheral sites, where it is metabolized by a glutathione reductase, resulting in the formation of a nitrite.[11] Nitrites convert oxyhemoglobin to methemoglobin.[4,12]

Oxyhemoglobin and methemoglobin normally occur in equilibrium in the body in a ratio of 99 to 1. This ratio may be altered by agents that increase the rate of oxidation (nitrates, sulfonamides, aniline dye derivatives) or in patients that are deficient in the enzyme necessary for reducing methemoglobin.[9,13,14]

Although NTG-induced methemoglobinemia has been reported,[1–3] the incidence and significance of this finding has been questioned in patients receiving clinically effective doses of nitrates.[15,16] The results from our study suggest that clinically significant methemoglobinemia is rare when the usual doses of i.v. NTG are used. Patients who receive i.v. NTG have higher than normal arterial methemoglobin levels, and these levels are positively correlated with the amount of i.v. NTG received; however, none of our patients had levels that approached those necessary to cause symptoms. Nevertheless, the development of abnormally elevated methemoglobin levels can reduce oxygen-carrying capacity and, thus, potentially precipitate or aggravate tissue ischemia.

In conclusion, clinically significant methemoglobinemia associated with i.v. NTG administration is uncommon; however, it should be considered when large amounts of NTG are administered, especially in association with other oxidizing agents.

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Incomplete and Delayed Bioavailability of Sublingual Nitroglycerin

PATRICK K. NOONAN, PhD, and LESLIE Z. BENET, PhD

Eight healthy male volunteers received 16 doses of sublingual nitroglycerin tablets (0.4 mg). After 8 minutes, each subject rinsed out his mouth to halt the drug absorption process. The mouth rinses were assayed by high-performance liquid chromatography for residual nitroglycerin content. Each subject also received intravenous infusions of nitroglycerin so that the absolute bioavailability could be evaluated. Plasma nitroglycerin concentrations were determined using a specific and sensitive capillary gas chromatographic method capable of quantifying 25 pg/ml of nitroglycerin. The mean bioavailability (± standard deviation) of sublingual nitroglycerin, estimated from plasma concentrations, was 36.2 ± 24.9% (range 2.6 to 113%). The amount of drug not absorbed after 8 minutes, as determined from the analysis of the mouth rinses, varied from 2.7 to 65.8% (mean 31.4 ± 18.9%) of the administered sublingual dose. Mean nitroglycerin peak concentrations of 1.89 ± 1.64 ng/ml were obtained at a mean peak time of 5.3 ± 2.3 minutes. Thus, sublingual absorption is not instantaneous and can be relatively slow, with peak times of as long as 10 minutes. These data indicate that nitroglycerin pharmacokinetic values should not be estimated only from sublingual doses. Additionally, attempts to correlate pharmacodynamic measurements to sublingual doses must take into account the low and variable bioavailability and the potentially long peak times after sublingual nitroglycerin administration to patients.

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Sublingual nitroglycerin is used most often for the acute relief of angina pectoris. Other investigators, when evaluating nitroglycerin pharmacokinetics, have assumed that sublingual nitroglycerin is instantaneously and completely bioavailable. Armstrong et al[1] made these assumptions when they calculated the clearance and volume of distribution of nitroglycerin from a single sublingual dose. Other researchers have used sublingual nitroglycerin as the relative bioavailability standard for other nitroglycerin dosage forms.[2,3] The "absolute" bioavailability of sublingual nitroglycerin has not been evaluated.

Methods

Eight healthy male volunteers received sublingual tablets (0.4 mg) of nitroglycerin (Nitrostat®, Parke-Davis) obtained from the hospital pharmacy of the University of California, San Francisco. All doses were obtained from 2 bottles of the same manufactured lot (JBATMA). At 0 time, a 0.4-mg nitroglycerin tablet was placed under the subject's tongue. Two drops of distilled water were added to the tablet to insure that the tablet was moistened. The subjects were instructed to maintain the tablet in the sublingual area and not to swallow it. After 8 minutes, the subjects were instructed to spit out any remaining dose, including saliva, into a glass container. Each subject then rinsed out his mouth with 50 ml of distilled water. This maneuver essentially halts the drug absorption process. The water rinse was added to the 8-minute saliva collection and assayed by high-performance liquid chromatography (HPLC) for residual nitroglycerin content. Six of the 8 volunteers received sublingual tablets on 2 different occasions, and 2 of these 6 volunteers also received a third dose.

For each sublingual dose, serial blood samples were collected at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12.5, 15, 17.5, 20, 25, 30, 45, 60, 120, 180, 240 and 360 minutes. The blood samples were immediately processed[4] and the plasma was frozen in a dry-ice bath.

Each of the 8 subjects also received intravenous infusions of nitroglycerin so that the absolute bioavailability could be evaluated. Tridil® (American Critical Care), used for the infusions, was prepared as a 100-μg/ml solution in 5% dextrose in water. Nitroglycerin was delivered through a Tridilset® (American Critical Care), which adsorbs less than 1% of a nitroglycerin dose.[5] The dose was delivered as a constant infusion using a Harvard infusion pump and a sterile 50-ml glass

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Address for reprints: Leslie Z. Benet, PhD, Department of Pharmacy, 926 Medical Sciences Building, University of California, San Francisco, California 94143.

TABLE I Nitroglycerin Pharmacokinetic Measurements from Eight Volunteers Who Received Intravenous Infusions of Nitroglycerin

Subject	Infusion Rate (μg/min)	C_{ss} (ng/ml)	Clearance (l/min)	$T_{1/2}$ (min)
DD	38.5	5.20	7.41	3.2
JK	44.4	3.60	12.33	1.5
JW	39.4	1.64	24.10	2.5
MD	19.8	1.25	15.82	2.7
PL	40.6	2.08	19.49	2.4
RD #1	38.2	5.19	7.36	2.8
RD #2	36.6	5.71	6.41	1.4
SS	38.3	2.34	16.37	1.8
TM	54.0	4.02	13.44	2.2
Mean	...	3.45	13.64	2.3
±SD	...	±1.69	±6.00	±0.6

C_{ss} = steady-state nitroglycerin plasma concentration; SD = standard deviation; $T_{1/2}$ = drug half-life.

syringe. The dose was administered through a Teflon® obturator set placed in a peripheral arm vein. Blood samples were drawn through a heparin lock placed in a peripheral vein of the opposite arm, kept patent with periodic injections of heparin (67 USP units/ml) in saline solution.

Sublingual bioavailability comparisons were made relative to a planned 40-μg/min infusion rate. Two volunteers received a 40-μg/min infusion over 100 minutes. Five volunteers received a 40-μg/min infusion over 40 minutes, which was preceded by a 10-μg/min infusion for 40 minutes and a 20-μg/min infusion for 40 minutes. One subject (MD), who became hypotensive at a dose of 40 μg/min, was studied while receiving an infusion of 20 μg/min, which was preceded by a 10-μg/min infusion for 40 minutes. The infusion rate was determined in each study by assay of the infusion solution delivered by the syringe over a fixed time interval. Blood samples were drawn at 10, 20, 30 and 40 minutes after the infusion rate was established. At the conclusion of the infusion, blood samples were drawn at 1, 2, 4, 6, 10, 15, 20, 40, 60, 120, 180 and 240 minutes to determine the half-life of the drug.

Plasma nitroglycerin concentrations were measured using a specific and sensitive capillary gas chromatographic method[4] capable of quantifying 25 pg/ml nitroglycerin (coefficient of variation [CV] = 7.6%) using 1.0 ml of plasma. The nitroglycerin content of the sublingual tablets and the mouth rinses was determined using a modification of our published HPLC assay.[6] The prepacked column (Altex 5 micron, octyl (C_8), 4.6 × 150 mm) was eluted with acetonitrile:water (40:60, v/v) at a flow rate of 160 ml/hour.

Results

The average steady-state nitroglycerin plasma concentration and the measured infusion rate in each of the 8 subjects are listed in Table I, together with the clearance and half-life of the drug. Clearance after intravenous dosing is calculated as the infusion rate divided by the average steady-state plasma concentration. Marked intersubject variability in clearance is seen (CV = 44%), although good reproducibility was found in subject RD (CV = 9.8%), who was studied twice. The average nitroglycerin half-life was 2.3 ± 0.6 minutes.

Pharmacokinetic values for nitroglycerin after 16 sublingual administrations in the 8 volunteers are listed in Table II. Peak time showed marked inter- and intrasubject variability and averaged 5.3 min. Peak plasma concentration showed even greater variability (CV = 87%). Mean half-life (2.5 min) was similar to that found following intravenous dosing. The sublingual bioavailability (%F) for each dose of nitroglycerin was calculated as $(CL_{iv} \cdot AUC_s/DOSE_s) \times 100$, where CL_{iv} = the clearance determined from the intravenous infusion and AUC_s and $DOSE_s$ = the area under the plasma concentration-time curve and dose, respectively, after sublingual administration.

Because subject RD received intravenous infusions 2 times, Table II shows 2 sets of values for each sublingual dose in this subject. Calculated nitroglycerin bioavailability in all subjects ranged from 2.6 to 113%. Mean values and standard deviations are calculated using the 16 sublingual doses in the 8 subjects. Mean values did not differ markedly when only the average

TABLE II Pharmacokinetic Measurements from Each Volunteer After Sublingual Nitroglycerin Administration

Subject	T_{peak} (min)	C_{peak} (ng/ml)	$T_{1/2}$ (min)	AUC (ng·min/ml)	F (%)	Mouth Rinse (% Dose)	Total Dose Accounted For (%)
DD	4.0	3.01	2.8	19.25	35.6	2.7	38.3
JK #1	3.2	6.10	2.2	36.65	113.0	18.5	131.5
JK #2	4.0	5.12	2.4	20.28	62.5	13.3	75.8
JW #1	10.0	0.22	2.8	1.97	11.9	65.8	77.7
JW #2	8.0	0.87	2.6	7.18	43.3	60.0	103.3
JW #3	3.0	1.23	1.4	7.39	44.5	61.5	106.0
MD #1	6.0	1.26	1.8	8.39	33.2	24.3	57.5
MD #2	5.0	0.78	2.0	6.82	27.0	13.8	40.8
PL #1	5.0	1.50	2.0	8.18	39.8	22.0	61.8
PL #2	5.0	1.02	3.0	8.11	39.5	30.5	70.0
RD #1	10.0	0.80	2.8	6.87	12.8/11.0	44.5	57.3
RD #2	6.0	2.90	3.0	26.80	49.4/43.0	11.8	61.2
RD #3	2.0	1.61	2.3	8.47	15.6/13.6	41.6	57.2
SS #1	4.0	1.52	2.2	9.43	38.6	34.8	73.4
SS #2	4.0	1.72	2.4	12.50	51.2	29.0	80.2
TM	5.0	0.60	5.0	7.85	2.6	29.0	31.6
Mean	5.3	1.89	2.5	12.26	38.5	31.4	70.2
±SD	±2.3	±1.64	±0.8	±9.03	±25.6	±18.9	±26.3

AUC = area under plasma concentration-time curve; F = sublingual bioavailability; SD = standard deviation; $T_{1/2}$ = half-life; T_{peak} = time at which peak concentration (C_{peak}) was measured.

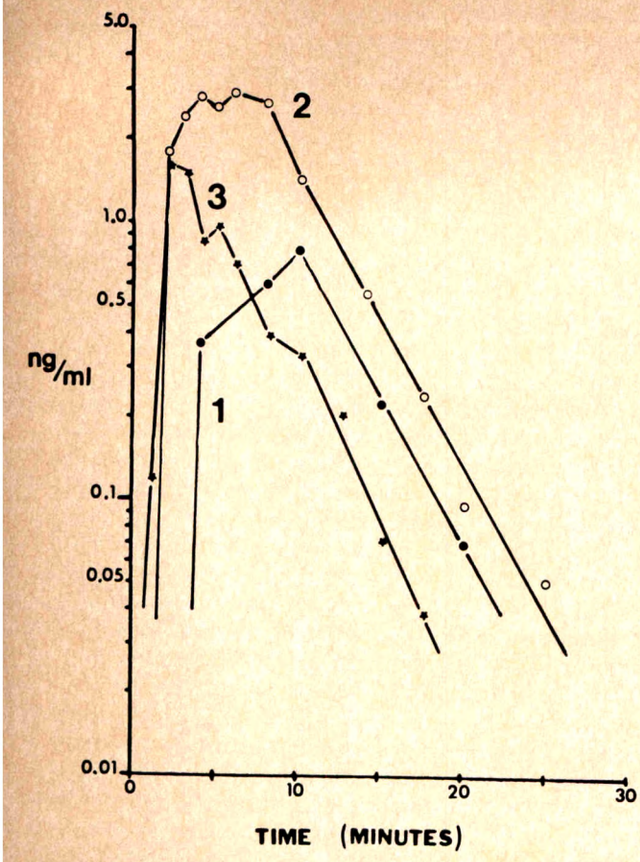

FIGURE 1. Nitroglycerin plasma concentrations after administration of a sublingual nitroglycerin tablet (0.4 mg) on 3 occasions to subject RD. The residual dose was washed out of the mouth 8 minutes after drug administration. Numerical identification corresponds to the data in Table II.

value for each subject was used in determining the means (e.g., %F = 37.5 ± 23.9). Figure 1 illustrates the marked intrasubject variability after sublingual administration on 3 different occasions.

The percent of dose measured in the mouth rinse ranged from 2.7 to 65.8% (average 31.4 ± 18.9%). Because this measurement is independent of other pharmacokinetic variables, one may conclude that sublingual dosing in this study does not yield a completely bioavailable dose of nitroglycerin. The last column in Table II is the summation of the calculated bioavailability and the measured drug in the mouth rinse. On average, 70% of the dose could be accounted for by these 2 variables, with a range from 32 to 132%. The CV for the summed parameter (37%) was less than that for the bioavailability (66%) and mouth-rinse measurements (60%). In fact, the variation in the total dose accounted for (last column, Table II) tends to reflect intersubject more than intrasubject variability. For subject RD, both bioavailability and mouth-rinse contents vary 4-fold, although the total dose accounted for remains quite constant.

Nitroglycerin tablets from each bottle were tested for potency using the HPLC assay[6] (Table III). There was no significant difference in the potency of tablets from

TABLE III Potency of 0.4-mg Nitroglycerin Tablets Obtained from Two Different Bottles of the Same Manufactured Lot

Sample	Replicate	GTN (mg)	Mean ± SD
Bottle A	1	0.51	
	2	0.44	
	3	0.42	0.44 ± 0.05
	4	0.37	
	5	0.44	
Bottle B	1	0.43	
	2	0.41	
	3	0.39	
	4	0.32	0.40 ± 0.04
	5	0.39	
	6	0.45	

GTN = nitroglycerin; SD = standard deviation.

the 2 bottles. Therefore, the low bioavailability values in the subjects in this study may not be attributed to decreased tablet potency.

Discussion

The "absolute" bioavailability of sublingual nitroglycerin has not been evaluated previously. This is partly because of the uncertainty of measurements after intravenous dosing, which must be used as the bioavailability standards. The clearance values reported here (13.6 ± 6.0 liters/min, Table I) after intravenous dosing far exceed the maximum possible hepatic clearance (1.5 liters/min). Such high clearance values suggest that nitroglycerin is cleared (metabolized) by organs other than the liver. The values reported here are only about one-fourth of the extremely high venous clearance values reported by McNiff et al[7] after an 18-μg/min infusion for 32 minutes and approximately twice the arterial clearance reported by Armstrong et al[8] after a 21-μg/min infusion for 120 minutes.

However, the clearance values determined in the present study appear to give reasonable estimates of bioavailability. If we had found a clearance equal to that reported by McNiff et al,[7] bioavailability measurements would have averaged approximately 160% and total dose accounted for would have been twice the dose. The lower clearance values recently reported by Armstrong et al[8] were determined in arterial samples from patients with congestive heart failure. Both of these conditions might be expected to yield a lower clearance value; for example, patients with heart failure often have decreased drug clearance compared with normal volunteers,[9] and there is an arteriovenous nitroglycerin gradient with an extraction of about 60%.[10] Armstrong et al[10] reported arterial nitroglycerin clearance rates (13.9 ± 8.7 liters/min) in patients with heart failure almost identical to those reported herein (13.6 ± 6.0 liters/min). The differences between the values discussed above as well as possible changes in nitroglycerin clearance as a function of infusion rate and total infusion time will be addressed in another report. The times to peak nitroglycerin concentrations ranged from 2 to 10 minutes. Since these peak times range from 1 to 5 times the half-life of nitroglycerin, the absorption of a sublingual dose cannot be assumed to be instantaneous. Therefore,

estimates of the volume of distribution of nitroglycerin that assume instantaneous input of a sublingual dose will certainly be in error.

On average, 70% of the sublingual dose was accounted for as bioavailable systemic concentrations plus residual dose in the mouth (Table III). Several factors could contribute to the average 30% that was not measured: (1) Although the subjects were instructed not to swallow during the 8 minutes the tablet was in the sublingual area, this variable was not controlled. Any drug that was swallowed would be metabolized before absorption. (2) Metabolism of the drug could take place in the mucous membranes of the mouth. (3) Differences in nitroglycerin clearance may be found between the intravenous infusion doses and the sublingual administration. Previously reported data[7,8,10] and our own unpublished studies indicate that the clearance may initially appear higher than that observed after a steady state is reached. Considering these factors, the 70% value probably indicates that the method used in this study reasonably describes nitroglycerin disposition after sublingual dosing. In addition, the value for only 1 of the 16 doses is markedly greater than 100% (subject JK, dose 1).

The inter- and intrasubject variation in bioavailability may be due simply to large variability in the absorption of nitroglycerin. No difference in bioavailability was noted between tablets from the 2 bottles used, and the contents of the tablets were as labeled (Table III). Crabbs et al[11] reported that sublingual nitroglycerin tablets, with acceptable disintegration characteristics, showed slow dissolution properties. Although some tablets were completely dissolved within 2 minutes, others were still not completely dissolved after 80 minutes in the dissolution apparatus. Nitroglycerin dissolution rate will certainly play an important role in defining the rate and extent of the bioavailability of sublingual nitroglycerin tablets. Many factors independent of the dosage form may play a role in the sublingual absorption of drugs: blood flow to the sublingual membranes; the ability of the volunteer (patient) to maintain the dose in the sublingual area without swallowing; and the hydration state of the sublingual area (i.e., dry mouth), which has been reported to affect the sublingual absorption of drugs.[12]

In conclusion, this study indicates that the bioavailability of sublingual nitroglycerin may be low and variable. A substantial portion of the administered sublingual dose was recovered from the mouth rinses after 8-minutes contact time with the sublingual membranes. These data indicate that nitroglycerin pharmacokinetic values should not be estimated only from sublingual doses of nitroglycerin. Additionally, attempts to correlate pharmacodynamic measurements to sublingual doses must take into account the low and variable bioavailability and the potentially long peak times after sublingual nitroglycerin administration to patients.

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Validation in Dogs of a Rapid Digital Angiographic Technique to Measure Relative Coronary Blood Flow During Routine Cardiac Catheterization

JOHN McB. HODGSON, MD, VICTOR LeGRAND, MD, ERIC R. BATES, MD, G. B. JOHN MANCINI, MD, FRED M. AUERON, MD, WILLIAM W. O'NEILL, MD, SANDRA B. SIMON, MA, GLENN J. BEAUMAN, MS, MICHAEL T. LeFREE, BS, and ROBERT A. VOGEL, MD

Assessment of the functional significance of anatomically defined coronary stenoses has been hampered by the lack of clinically applicable techniques of measuring coronary blood flow or flow ratios. A digital angiographic technique is reported that allows rapid analysis of relative regional coronary blood flow during routine cardiac catheterization. This technique was validated in dogs by comparing digital flow ratio estimates with electromagnetic-flow (EMF) ratio measurements. Fourteen open-chest dogs had EMF probes placed on the proximal left anterior descending artery before selective coronary angiography. Electrocardiographically gated images were acquired directly by a digital radiographic system during both baseline blood flow and either contrast or papaverine-induced hyperemia. Dual-parameter functional images were generated using color and intensity coding to represent contrast arrival time and contrast density, respectively. For analysis, myocardial areas of interest were created over the distal perfusion bed of the left anterior descending coronary artery. Mean contrast density/appearance time (CD/AT) values were computer calculated as the mean density divided by the mean arrival time for each. Coronary flow reserve was determined as the ratio of the CD/AT value for a hyperemic image divided by the CD/AT value for the corresponding baseline image. CD/AT ratios correlated well (r = 0.92) with actual EMF ratios (CD/AT Ratio = 0.90 EMF Ratio + 0.12, n = 48 ratios). Reproducibility was ±13%. Interobserver (r = 0.99) and intraobserver (r = 0.98) variability was excellent. Thus, rapid, accurate and reproducible estimates of relative regional coronary blood flow are possible using digital radiography. (Am J Cardiol 1985;55:188–193)

Although selective coronary arteriograms have long been the standard means of defining coronary anatomy, until recently little additional information has been available from these images. Our laboratory has described a digital angiographic technique that provides information on relative coronary blood flow and can be performed during routine cardiac catheterization.[1] Electrocardiographically gated (ECG-gated) digital images from successive cardiac cycles were used to generate dual-parameter functional images, termed contrast medium appearance pictures (CMAP). In these images, myocardial contrast appearance time is color coded, and was originally considered to be inversely proportional to blood flow. Our validation study used atrial pacing to induce hyperemia. The amount of flow during hyperemia was divided by the amount of basal flow to create coronary flow reserve ratios, and a good correlation between contrast appearance time ratios and coronary sinus blood flow ratios was demonstrated (r = 0.90) in humans.

Since that report, the technique has been refined. With current techniques, digital images are stored directly on a digital disk allowing immediate analysis without the need for initial film storage and subsequent digitization. ECG-gated power injection and atrial

From the Cardiology Section, Veterans Administration Medical Center, Ann Arbor, Michigan. This study was supported in part by research grants from the Veterans Administration, Washington, D.C. and Michigan Heart Association, Lathrup Village, Michigan. Manuscript received June 15, 1984; revised manuscript received August 31, 1984, accepted September 4, 1984.

Address for reprints: Robert A. Vogel, MD, Chief, Cardiology Section, Veterans Administration Medical Center, 2215 Fuller Road, Ann Arbor, Michigan 48105.

pacing are now used routinely. In addition, either contrast or papaverine are used to induce hyperemia. In this report we describe the improved technique and further validation in instrumented dogs.

Methods

Animal preparation: Fourteen mongrel dogs of either sex that weighed 25 to 44 kg (average 32) were anesthetized with intravenous pentobarbital (35 mg/kg) and ventilated with room air using a Harvard respirator. A left thoracotomy was performed. Right atrial epicardial pacing electrodes were placed after the sinus node and accessory pacemaker cells were ablated by intramyocardial infiltration of a 50/50 mixture of absolute alcohol and 0.5% Marcaine® solution. This allowed atrial pacing at heart rates of less than 130 beats/min. The proximal left anterior descending coronary artery was dissected free, and an appropriately sized electromagnetic flow (EMF) probe (Carolina Medical Electronics, model EP200®) and pneumatic cuff occluder were placed. The EMF was calibrated by timed collection and corrected for hematocrit. Selective coronary catheterization was performed using a 7Fr Amplatz catheter introduced retrogradely through a right femoral artery sheath under fluoroscopic guidance.

Image acquisition: Atrial pacing was used throughout image acquisition at a rate just above the intrinsic rate. Images were stored directly on a digital disk using ECG-gated cineradiographic mode acquisition, fixed kilovoltage, amperage, pulse width (approximately 70 kV, 200 mA, and 5 ms, respectively), and logarithmic analog-to-digital conversion. The image matrix was 512 × 512 × 8 bits. Imaging was performed with cineradiographic equipment (Philips model Optimus M200) interfaced directly to a digital radiographic computer (ADAC, model DPS-4100). All image acquisition was ECG gated to provide 2 images per cardiac cycle at 50% and 75% of the RR interval (intended to correspond to cardiac diastasis). Full-strength sodium meglumine diatrizoate (Renografin 76®, Squibb & Sons) was injected using an ECG-gated angiographic power injector (Mark IV®, Medrad). Three milliliters were delivered at 3 ml/s for all image acquisitions. Images were obtained during baseline flow (obtained at least 3 minutes after previous contrast administration) and during hyperemia induced by intracoronary contrast injections (0.5 to 5 ml) 10 to 15 seconds before imaging (n = 29), or intracoronary papaverine (5 mg) delivered 30 to 45 seconds before imaging (n = 3).

Image processing: Images were processed by mask-mode subtraction. The last single frame before contrast administration was chosen as the mask. Five to 8 successive diastolic images were selected as the image subset (1 per cardiac cycle), and standard mask-mode subtraction was accomplished. Dual-parameter functional images were then generated using a threshold (8%) criterion, which assigns pixel color based on the number of cardiac cycles after injection at which the given pixel density must exceed the threshold. Red was assigned to pixels that had an intensity that surpassed the threshold in the first postinjection cycle, yellow for the second cycle, white for the third, green for the fourth, and so on. All studies from a dog were generated using the same number of images. The intensity of each pixel in the functional image was defined by the maximal density achieved during that series.

Image analysis: Regional flow ratios were quantitatively determined from CMAP pairs using the videodensitometric[2,3] principle:

$$\dot{Q} = \frac{RVV}{t} \quad (1)$$

where $\dot{Q}$ = regional blood flow, RVV = regional vascular volume, and t = transit time. This laboratory initially used the assumption that regional vascular volume (RVV) remained constant under baseline and hyperemic conditions. Under this

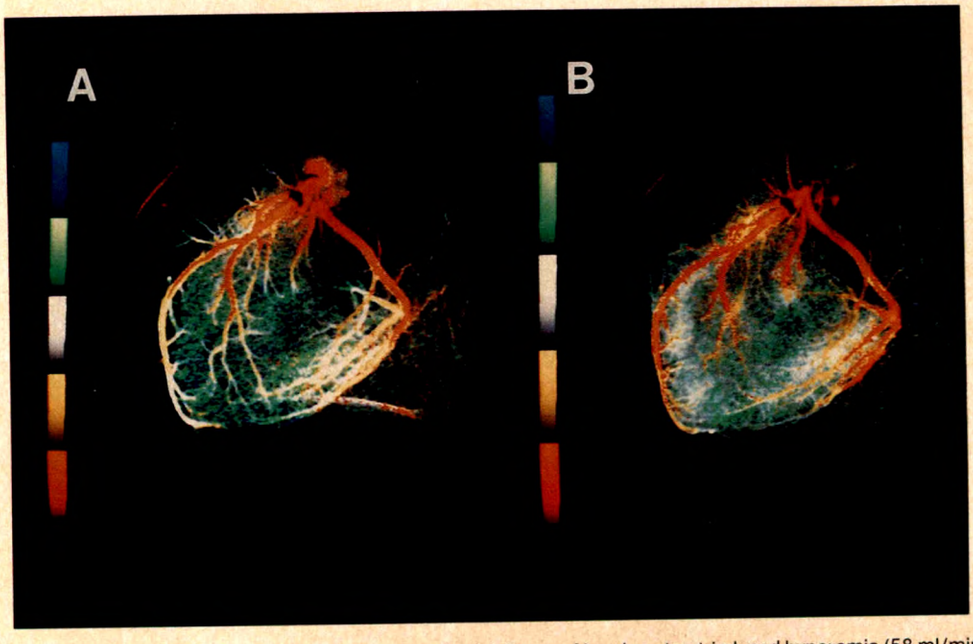

FIGURE 1. Functional images from a dog during baseline flow (27 ml/min) (**image A**) and contrast-induced hyperemia (58 ml/min) (**image B**). Note the earlier colors and greater intensity over the distribution of the left anterior descending artery in **image B.** The appearance time (AT) value for **image A** is 1.89 second and that for **image B** is 1.26 second. The contrast density/appearance time (CD/AT) values are 0.13 and 0.29, respectively. The flow reserve ratio determined by electromagnetic flow probe is 2.15. The flow reserve ratio measured digitally is 1.50 using the AT values alone and 2.23 using the CD/AT values.

assumption, $\dot{Q}_h/\dot{Q}_b$ was determined using mean arrival time (AT) as the transit time parameter:

$$\frac{\dot{Q}_h}{\dot{Q}_b} = \frac{RVV/AT_h}{RVV/AT_b} = \frac{AT_b}{AT_h} \quad (2)$$

This approach yielded a close correlation between pacing-induced hyperemic-to-baseline flow ratios measured by digital radiography and thermodilution measurements of coronary sinus and great cardiac vein blood flow.[1] Application of this principle to contrast medium–induced hyperemic-to-baseline blood flow ratio determinations, however, yielded substantial underestimation of high flow ratios. This was attributed to RVV increases caused by the hyperemia-inducing stimulus. Therefore, we estimated RVV using logarithmic mask-mode subtraction[4,5] and the equation:

$$RVV = \frac{k}{c} \int D \quad (3)$$

where k = radiographic constant, c = contrast medium concentration, and D = radiographic density. The radiographic constant (k) is a function of the attenuation coefficient of the iodine medium, the transfer function of the image intensifier and plumbicon, the radiographic parameters used, and the analog-to-digital conversion function.[6] For measurements of relative RVV changes under conditions of 100% contrast medium concentration, k and c cancel out. Similarly, if the same regions of interest are used for baseline and hyperemic conditions, mean contrast density (CD) can be substituted, yielding:

$$\frac{\dot{Q}_h}{\dot{Q}_b} = \frac{\frac{k}{c}\int D_h/AT_h}{\frac{k}{c}\int D_b/AT_b} = \frac{CD_h}{AT_h} \div \frac{CD_b}{AT_b} \quad (4)$$

Mean (arithmetic) contrast medium appearance time and density were computer histographically determined within operator-defined left anterior descending coronary artery areas of interest for each CMAP. These regions contained 3,000 to 5,000 pixels and were placed in such a way as to exclude the large epicardial arteries, the aortic root and the coronary sinus. Equivalent regions were chosen for each picture pair. Only the studies obtained within 10 minutes of each other were used for flow ratio determinations. Hyperemia-to-baseline and baseline-to-baseline flow ratios were calculated using equation 4 and were compared to EMF flow ratios of mean values obtained at the onset of injection. Because the CMAP analysis yields appearance time in cardiac cycle units, these values were converted to seconds using the cycle length. In this calculation, pixels appearing in the first cardiac cycle after contrast administration were assigned an AT of 0.5 cycles, those in the second cycle an AT of 1.5 cycles, and so on.

Statistical analysis: Least-squares linear regression was used to compare the digital AT and CD/AT ratios and the actual EMF ratios. Reproducibility was assessed by comparing ratios of successive baseline images and was calculated as the mean difference between corresponding AT ratios and EMF ratios divided by the mean EMF ratio for all comparisons. Inter- and intraobserver variability were calculated as the standard error of the estimate (SEE) of a least-squares linear regression comparing sequential observations.

Results

Animal validation: Figure 1 shows 2 functional images from the same dog. Image A was obtained at baseline blood flow (27 ml/min) and image B during contrast-induced hyperemia (58 ml/min). The AT value for image A is 1.89 s and for image B 1.26 s. The CD/AT value for image A is 0.13 and for image B 0.29. The EMF coronary flow reserve ratio is 2.15. The coronary flow reserve ratio measured digitally is 1.5 using AT data alone, but 2.23 using the CD/AT ratio.

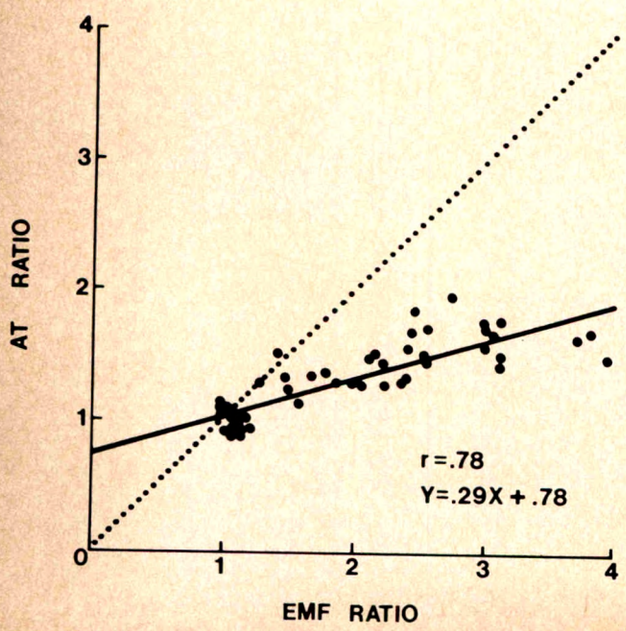

FIGURE 2. Correlation of coronary flow reserve ratios measured by electromagnetic flow (EMF) probe and ratios calculated from digital estimates using appearance time (AT) (in seconds) only. Despite a fair correlation, digital AT ratios considerably underestimated true flow ratios.

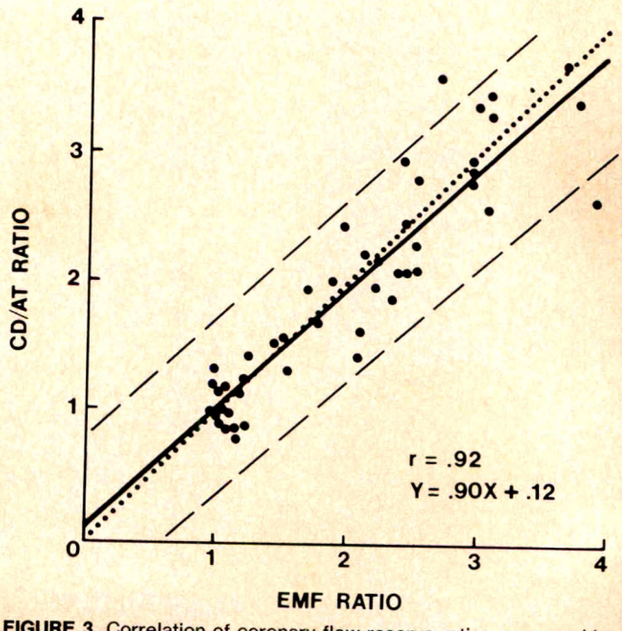

FIGURE 3. Correlation of coronary flow reserve ratios measured by electromagnetic flow (EMF) probe and ratios calculated digitally using both contrast density and appearance time (CD/AT) (in seconds) information. Confidence limits (95%) are represented by the **dashed lines.** Digital CD/AT ratios correlated well with EMF ratios and were more accurate than appearance time ratios alone.

TABLE I Results of Successive Baseline Blood Flow Determinations

Pair No.	EMF Ratio	CD/AT Ratio	EMF − CD/AT
1	1.00	1.00	0
2	1.00	1.05	0.05
3	1.04	1.17	0.13
4	1.04	0.93	0.11
5	1.04	0.93	0.11
6	1.10	0.86	0.24
7	1.11	1.18	0.07
8	1.05	0.88	0.17
9	1.17	1.40	0.23
10	1.10	1.39	0.29
11	1.14	1.10	0.14
12	1.00	1.36	0.36
13	1.09	1.01	0.08
14	1.05	0.91	0.14
15	1.00	1.02	0.02
Mean	1.06	1.08	0.14

Variability is 13.2% (mean EMF − [CD/AT]/mean EMF ratio).

Ratios of AT values for myocardial areas of interest showed a fair correlation with actual flow ratios ($r = 0.78$). Forty-eight ratios were obtained from a total of 65 images in the 14 dogs. Only CMAPs obtained within 10 minutes of each other were used for flow ratios (Fig. 2). The regression equation is $y = 0.29x + 0.78$, where y is the ratio of AT values and x the ratio of EMF values. Ratios of CD/AT values for myocardial areas of interest showed a better correlation with the actual flow ratios ($r = 0.92$) (Fig. 3). The regression equation is $y = 0.90x + 0.12$, where y is the ratio of CD/AT values and x the ratio of EMF values. Reproducibility was assessed by comparison of successive baseline images within each dog. The corresponding EMF and AT ratios are shown in Table I. Reproducibility was calculated as ±13.2%.

Interobserver variability is shown in Figure 4. Two observers separately and independently viewed 28 images and generated 22 AT ratios using the computer algorithm described previously. Correlation was excellent ($r = 0.99$). The regression equation is described as the AT of observer 2 = 0.98 × AT of observer 1 + 0.01. The SEE was 0.038. Intraobserver variability is shown in Figure 5. One observer viewed 28 images and generated 22 AT ratios using the computer algorithm on 2 occasions 2 weeks apart. An excellent correlation was found ($r = 0.98$). The regression equation is described as AT (reading 2) = 1.02 × AT reading of observer 1 − 0.03. The SEE was 0.049.

Discussion

Several methodologic changes in this digital radiographic approach to measuring relative regional coronary blood flow from that originally reported by this laboratory[1] should be emphasized: (1) The current hardware allows direct digital image acquisition without prior film storage. (2) Atrial pacing is used routinely to ensure a constant heart rate during image acquisition. (3) Contrast injections are carefully controlled for volume, rate of injection and timing by ECG-gated power injection. (4) Images are processed by mask-mode subtraction rather than gated interval difference, because motion artifact has been considerably reduced by atrial pacing and precise ECG gating. (5) Both density and appearance time information is utilized in image analysis. These changes have been incorporated into our current clinical catheterization method.

This technique for measuring relative regional coronary blood flow is founded on other inflow videodensitometric techniques,[2,3] but significant differences do exist. First, relative flow ratios rather than absolute flow values are produced, eliminating the need for absolute density measurements. Rather than use the indicator-

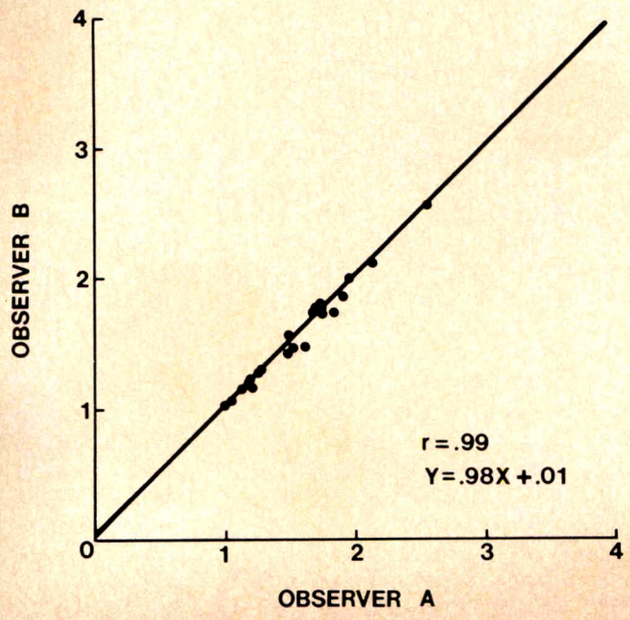

FIGURE 4. Interobserver variability. Observers A and B showed excellent agreement for appearance time ratios.

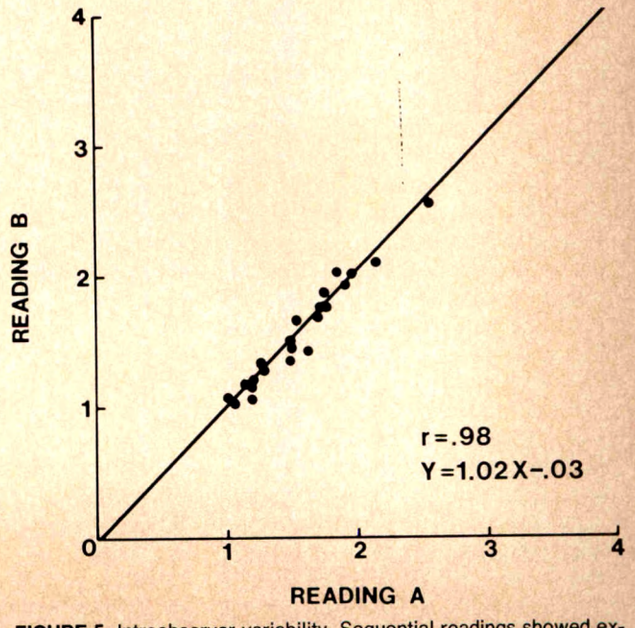

FIGURE 5. Intraobserver variability. Sequential readings showed excellent agreement for appearance time ratios.

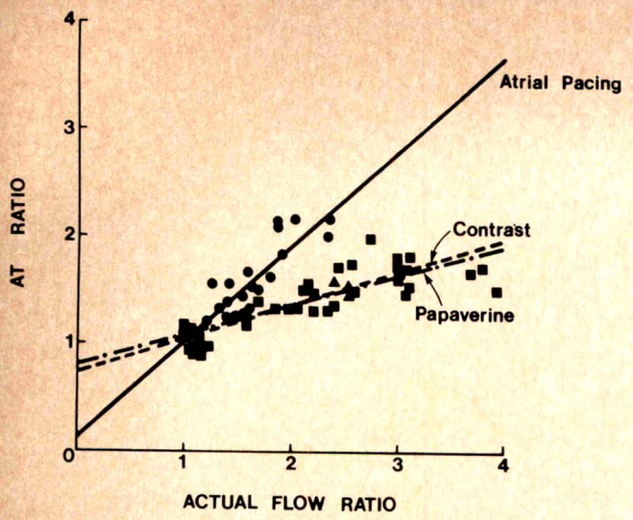

FIGURE 6. Comparison of appearance time (AT) ratios calculated for differing methods of inducing hyperemia. Actual flow ratios were calculated from coronary sinus flow measurements for atrial pacing and from electromagnetic flow measurements for both contrast and papaverine-induced hyperemia. Note the marked underestimation of actual flow ratios for both methods of pharmacologically induced hyperemia. The **circles** represent atrial pacing hyperemia; the **squares** represent contrast-induced hyperemia; the **triangles** represent papaverine-induced hyperemia.

dilution approach of Foerster et al,[6] which requires that a known or fixed amount of contrast be injected completely down the artery, we used a volumetric videodensitometric method. Second, these functional images can be generated within a few minutes of acquisition, allowing for repetition of studies with motion artifact. Third, this is the first method that uses myocardial regions of interest as suggested by Robb et al.[7] This allows the use of relatively large areas of interest (3,000 to 5,000 pixels), which can be placed in specific regional distributions at the discretion of the operator. Other techniques[2,3,6,8–10] require precise localization of small areas of interest over epicardial arteries and, in addition, require precise measurement of arterial diameter to obtain quantitative flow measurements.[2,3,9,10] The coronary anatomy in our images is used only as a guide to the placement of an appropriate myocardial area of interest. Although subject motion is the most important factor in CMAP quality, a small degree of misregistration does not appear to substantially affect the accuracy of flow ratio estimates. Fourth, precisely gated digital radiographic acquisition allows flow information to be generated using only 1 frame/cardiac cycle. Thus, radiation is reduced greatly compared with techniques that use 30 to 100 Hz acquisition.[2,3,6,8–10]

Several limitations should also be mentioned. Atrial pacing is necessary for accurate gating. The use of a power injector to deliver the contrast bolus is a complicating factor. However, we have not experienced any complications related to power injection in more than 200 patients. Other investigators[9–11] have also used power injection without complication. Finally, as with all digital subtraction techniques, patient motion can produce artifact.

Coronary blood flow was measured by EMF probe in this validation study. The observed mean maximal contrast-induced flow ratios (2.74, n = 13) are within the broad range of reported values determined by rotameter (2.14)[12] or EMF probe (3.7, 2.64).[13,14] EMF probes are dependent on close vessel probe contact. In all cases, our probes fit snugly and we observed no variation in the baseline (0 flow) determination between successive measurements. Blood flow measurements were made just before contrast medium injection, but the latter was not observed to have substantial effect on the flowmeter values during injection. We acquired images without removing the catheter from the coronary ostium and noted no impairment in coronary flow reserve. We observed prompt free reflux of contrast into the aorta on all injections, indicating that the catheter was not wedged and that the contrast flow rate was sufficient to achieve 100% contrast concentration within the artery. Other investigators also have found no differences between coronary flow measurements made with and those made without the catheter removed.[6,14–17]

This technique uses inflow (washin) transit-time analysis, the principle of which is described in equation 1.[2,3] In the original description of this technique,[1] the assumption was made that the volume of distribution remained constant. In that study, changes in coronary sinus blood flow were induced by atrial pacing and were inversely correlated with changes in digitally generated mean appearance times (r = 0.90). The slope of the regression equation was 0.79, suggesting that during flow increases induced by atrial pacing, the volume of distribution remained relatively constant. However, when contrast was used as a hyperemic stimulus for the present validation study, the volume of distribution did change during contrast-induced hyperemia. Figure 2 shows the underestimation of true contrast-induced hyperemic flow when appearance time alone was used to generate digital flow ratios. Despite a reasonable correlation (r = 0.78), the regression equation yielded a very low slope (0.29). Recruitment of capillaries,[18] capillary dilatation,[19,20] fluid shifts into the vascular compartment[21,22] and dilatation of epicardial arteries[23] have been observed during pharmacologically induced hyperemia. Actual measured total myocardial vascular volume also increase markedly after pharmacologic vasodilatation or hypoxia.[24–27] In these situations, where the distributional volume is increased, changes in coronary flow will be underestimated by changes in coronary flow velocity.[23] Because appearance time measures coronary flow velocity, it would be expected to underestimate flow after contrast-induced hyperemia (Fig. 2).

Würsten et al[28] showed that these volume changes can be measured directly by angiographic CD changes. Therefore, to correct the volume of distribution alterations, we used CD information. The CD/AT value (defined in equation 4) represents this corrected flow estimate. Because the absolute volume of distribution is not known, CD/AT values represent only relative and not absolute flow estimates. Figure 6 shows the relation between AT ratios and true flow ratios for several methods of inducing hyperemic flow. Atrial pacing

hyperemia is not underestimated by measurements of flow velocity alone, whereas both papaverine and contrast-induced hyperemic flow AT ratios show considerable underestimation of true flow changes. This substantiates our observation[1] that the intensity of myocardial blush on images obtained during contrast-induced hyperemia was much greater than that on images obtained during pacing-induced hyperemia.

Acknowledgment: We are grateful to Diane Bauer for preparation of this manuscript.

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Electrophysiologic and Anatomic Changes in the Atrioventricular Junction of Dogs After Direct-Current Shocks Through Tissue Fixation Catheters

MELVIN M. SCHEINMAN, MD, SAROJA BHARATI, MD, YIN-SHI WANG, MD, WILLIAM A. SHAPIRO, MD, and MAURICE LEV, MD

Barb-tipped fixation electrode catheters were inserted under fluoroscopic control in the region of the atrioventricular (AV) node in 6 dogs. A series of direct-current shocks (20 to 240 J) were delivered from the electrode catheter to a back plate. Serial electrophysiologic studies were performed before and 2 to 3 weeks after delivery of the shocks. In general, low-energy shocks—20 to 180 J—resulted in predominant damage to the approaches to the AV node, the AV node and common bundle, whereas larger shocks created diffuse damage involving the His bundle and bundle branches. Despite histologic damage to the AV junction, only minimal changes in AV conduction were observed. Thus, there is a large safety margin for AV conduction.

(Am J Cardiol 1985;55:194–198)

A technique for closed-chest catheter ablation of the atrioventricular (AV) junction has been recently described in dogs[1,2] and extended for clinical use.[3–5] This technique is limited because tachycardia control is achieved at the expense of pacemaker dependency. The objective of the present study was to assess the effects of electrical energy delivered through catheters fixed in the region of the AV node in order to create a model of impaired AV conduction without need for chronic pacing.

Methods

Six mongrel closed-chest dogs that weighed 25 to 35 kg were anesthetized with sodium pentothal and ventilated by a Harvard respirator. A standard no. 6 USCI quadripolar electrode catheter was positioned across the tricuspid valve for His bundle recordings. A separate electrode catheter was positioned against the high lateral right atrial wall for pacing. Either a modified USCI bipolar catheter with barbed tip or a Medtronic no. 6917 screw catheter was used. In 3 dogs, it was possible to cannulate the coronary sinus and the fixation catheter was inserted between catheters (Fig. 1) by means of biplane fluoroscopy. In 3 other dogs, the tissue fixation catheter was inserted just posterior and inferior to the site of the largest His deflection. Baseline AV conduction intervals were recorded, anterograde refractory periods were measured, and incremental atrial overdrive pacing (at 20-ms increments) was used to ascertain the minimal cycle length at which 1:1 AV conduction occurred. A plate lubricated with conduction gel was positioned behind the back between the scapulae. The distal electrode was used as a current source (cathode) and the back plate was used as the current sink (anode) from a Physio-Control defibrillator. This defibrillator was modified to deliver direct-current shocks in 20-J increments. The initial energy was 20 J and incremental shocks were delivered until second- or third-degree AV block was produced. The site of AV block was localized by His recordings. Return of 1:1 AV conduction occurred in all dogs within 35 minutes. The dogs were examined daily by a veterinarian with 2-minute surface electrocardiographic strips obtained 3 times per week. Studies of AV conduction were repeated at 2.5 weeks. Changes in the AV nodal refractory period could not be assessed in 4 dogs due to either achievement of atrial refractoriness or induction of rapid polymorphous unsustained atrial arrhythmias.

All dogs were killed after the repeat study for gross examination of the heart, coronary vessels and detailed examination of the cardiac conduction system.

Method of study of the conduction system: Blocks were taken from the sinoatrial node, AV node, bundle and bundle branches up to the moderator band. These blocks included the approaches to the sinoatrial and AV nodes. The blocks were serially sectioned. Every twentieth section was stained

From the Department of Medicine and Cardiovascular Research Institute, University of California, San Francisco, California, and the Congenital Heart and Lung Center, Browns Mills, New Jersey; Departments of Pathology, Temple University, Philadelphia, Pennsylvania, and Pennsylvania State University, Milton S. Hershey Medical Center, Hershey, Pennsylvania. This study was supported by Grant HL 30558-02 and HL 29267 from the National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received June 1, 1984; revised manuscript received September 14, 1984, accepted September 15, 1984.

Address for reprints: Melvin Scheinman, MD, Moffitt Hospital, Room 312, University of California, San Francisco, California 94143.

TABLE I Electrophysiologic Changes Before and After Shock

Pt	Sinus Rhythm		Atrial Pacing			
	AH	HV	Minimal CL with 1:1 AV Conduction	AH*	AVNERP	J
1 C	60	30	200	80	140	20
S	70	33	200	120	155	
2 C	40	35	200	90	<100†	140
S	50	30	240	130	<160	
3 C	52	37	220	85	<140†	180
S	50	40	240	120	<140	
4 C	40	25	200	90	120	180
S	49	29	200	. . .	. . .	—
5 C	50	30	210	85	120	200
S	53	30	240	110	140	
6 C	60	40	200	110	<120†	240
S	80	45	240	150	<120	
Mean ±SD	50 ± 9	33 ± 5	205 ± 8	90 ± 10		
Mean ±SD	58 ± 13	35 ± 7	227 ± 21	126 ± 15		
p value		NS	0.05	0.02	NS	

* AH interval at minimal paced cycle length.
† Precise AVNERP could not be determined because of either atrial refractoriness or induction of atrial tachycardia.
2 to 3 weeks after shock; AV = atrioventricular; AVNERP = atrioventricular nodal effective refractory period; C = control; CL = cycle length; NS = not significant; S = SD = standard deviation; — = His bundle deflection not well recorded during pacing; . . . = not recorded.

alternatively with hematoxylin-eosin and Weigert-Van Gieson stains. Approximately 1,200 sections were examined for each dog.

Results

The electrophysiologic findings are summarized in Table I. The amount of energy required to acutely produce second- or third-degree AV block varied from 20 to 240 J. With low-energy shocks (20 to 180 J), acute

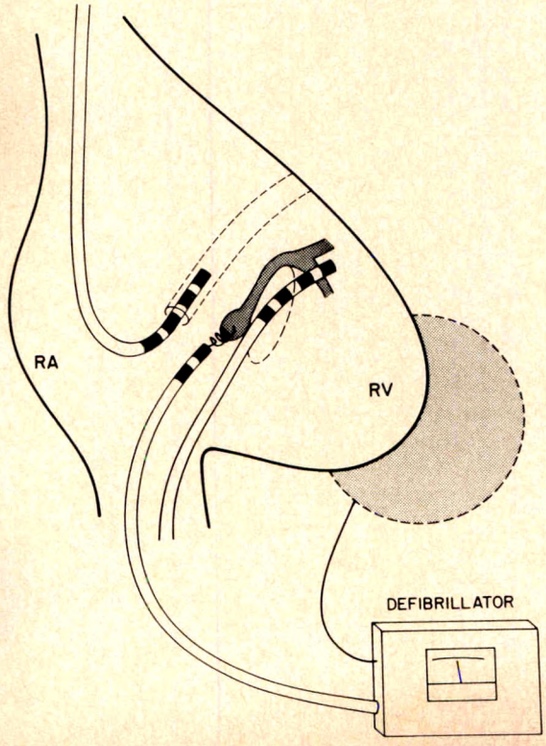

FIGURE 1. Placement of screw-in electrode in the vicinity of the atrioventricular node. RA = right atrium; RV = right ventricle.

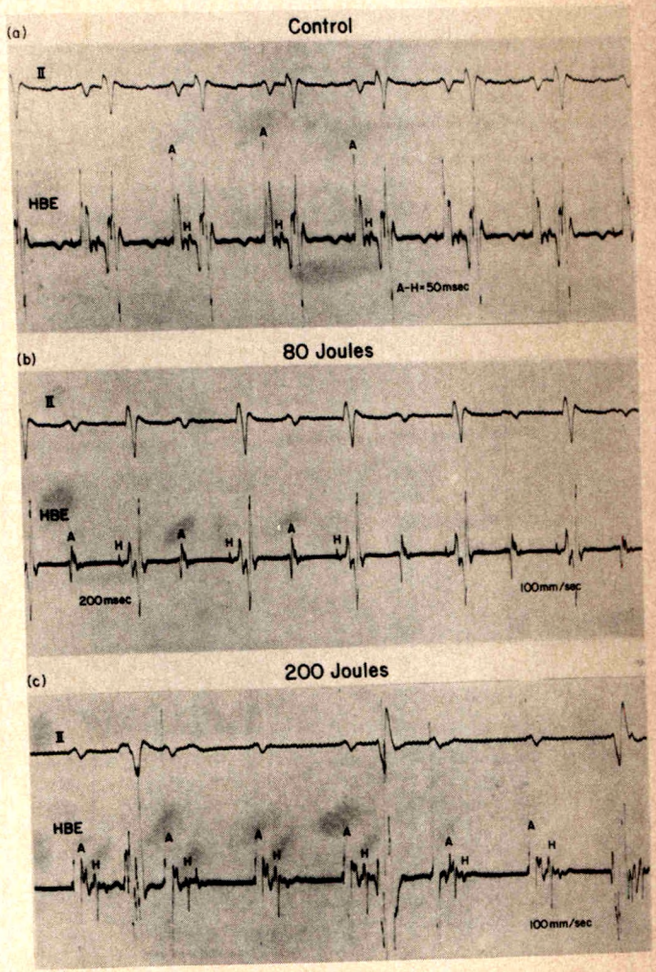

FIGURE 2. Simultaneous recordings of surface lead II and the His bundle electrogram (HBE) before (**a**) and after delivery of 80 J (**b**) and 200 J (**c**). After 80 J, first-degree AV block is localized to the level of the atrioventricular node as reflected by the marked lengthening of the AH interval. After delivery of a total of 200 J, complete infranodal block is apparent.

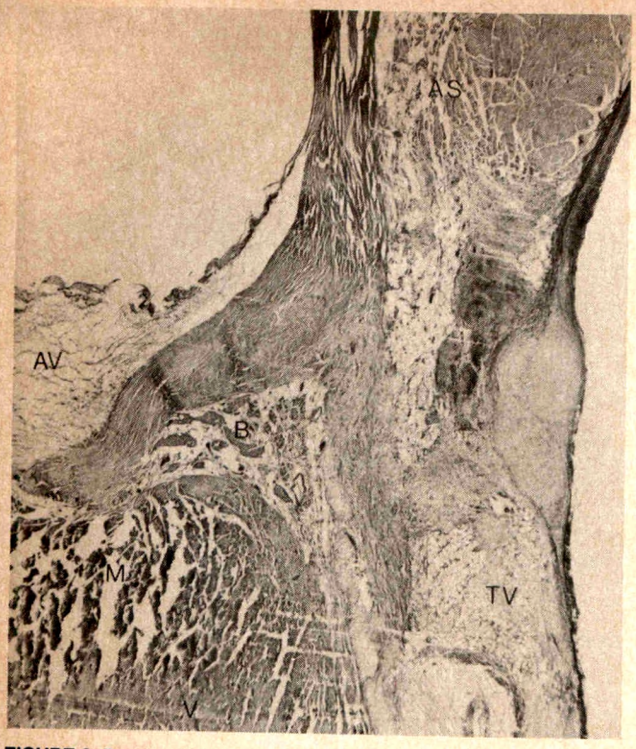

FIGURE 3. Bundle of His (B) in dog 1, showing dissolution of tissue and space formation. Also visible is degeneration of spongiosa of anulus of aortic valve (AV) and tricuspid valve (TV) and coagulative necrosis of some myocardial fibers (M) in summit of the ventricular septum (V). AS = atrial septum. Weigert-van Gieson stain; magnification × 30, reduced 27%.

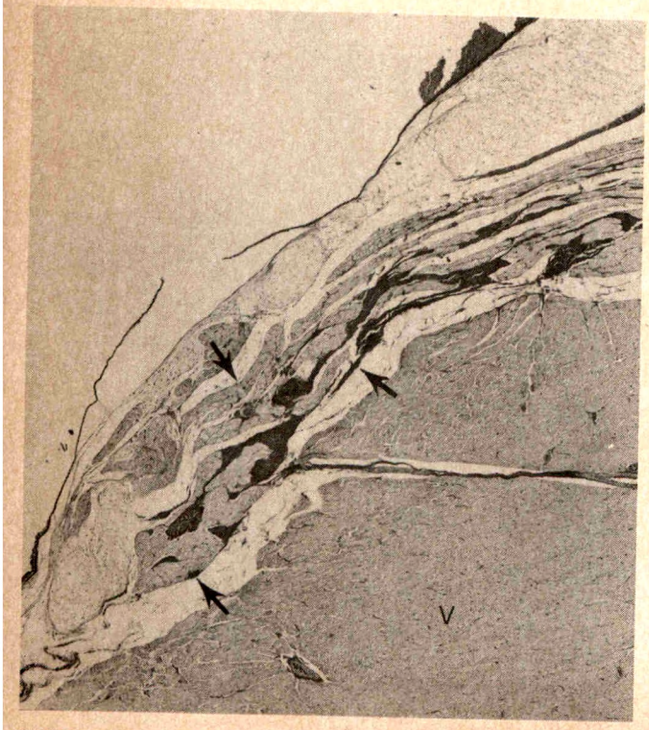

FIGURE 4. Fibrosis of beginning of left bundle in dog 4. **Arrows** point to left bundle. V = ventricular septum. Weigert-van Gieson stain; magnification × 45, reduced 23%.

AV block was always localized to the AV node. Higher-energy shocks (200 to 240 J) caused acute block both at the node and below the node. The sites of block immediately after shock were localized to the AV node in dogs 1 to 4, and were both AV nodal and infranodal in dogs 5 and 6. Physiologic infranodal block, because of AV nodal Wenckebach cycles, was not observed (Fig. 2). One-to-one AV conduction returned by 35 minutes in all dogs. Analysis of all follow-up electrocardiographic recordings showed 1:1 AV conduction with normal QRS width. Although a bundle branch block pattern was occasionally observed just after the shocks, none was apparent on the follow-up tracings.

There was no significant change in the baseline AV nodal (AH) or infranodal conduction (HQ) times before and 2 to 3 weeks after shock, but the minimal paced cycle lengths that produced 1:1 conduction increased significantly (from 205 ± 8 to 227 ± 21 ms, $p < 0.01$). In addition, in the 2 dogs who showed no change in this measurement, the AH interval was longer at the same paced cycle length. There was a significantly greater increase in the mean AH interval after shock (from 90 ± 10 to 126 ± 15 ms, $p < 0.01$) at the minimal atrial paced cycle length which resulted in 1:1 AV conduction. Changes in the AV nodal refractory period could be

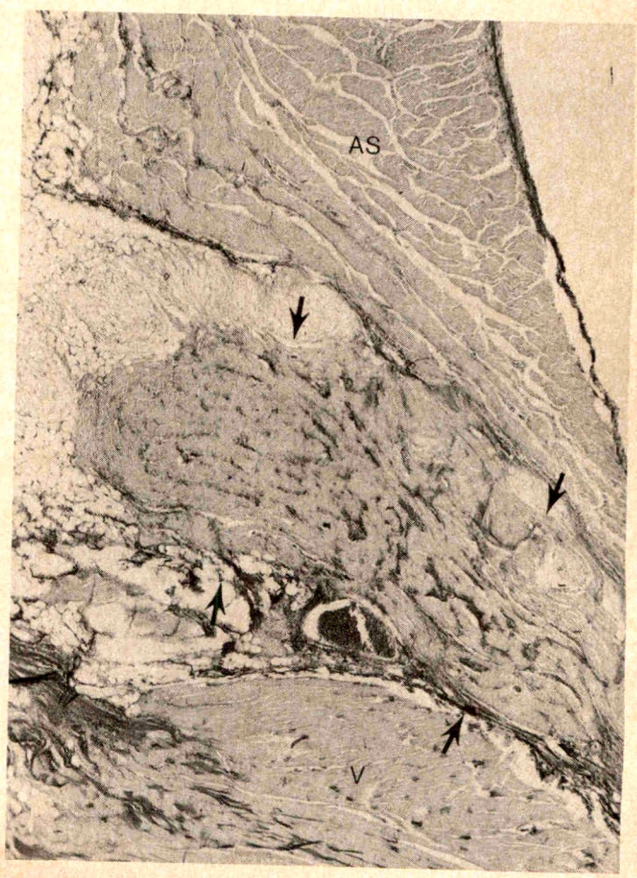

FIGURE 5. Atrioventricular node in dog 5, showing fibrosis (**arrows**). AS = atrial septum; V = ventricular septum. Weigert-van Gieson stain; magnification × 45, reduced 27%.

compared in 2 dogs, lengthening by 10 and 15 ms, respectively, after shock.

Atrial overdrive pacing failed to produce either increase in the HQ interval or infranodal conduction block. The effective refractory period of the His-Purkinje system was achieved in only dog 2, 2 weeks after shock. In all dogs, 1:1 AV conduction returned and remained stable over the 2- to 3-week observation period.

Gross examination of the heart: There was mild fibroelastosis seen in the AV node in dog 1. Marked thickening at the base of the septal leaflet of the tricuspid valve with focal fibrosis in the superior approaches to the AV node was present in dogs 2 to 6. The medial leaflet of the tricuspid was swollen in all. Otherwise, the hearts were normal at a gross level. The marked fibrosis observed in the region of the AV junction precluded assessment of anatomic location of the tissue-fixation catheters in relation to the AV node.

The amount of permanent injury produced in the approaches to the AV node, and the AV node in dogs 1 and 2 were mild and became somewhat more marked in the His bundle (Fig. 3) and bundle branches. In dog 3, damage was significant in the approaches to the AV node and the AV node itself, and became less in the His or common bundle and right bundle, but was severe in the left bundle with almost complete interruption of the beginning of the left bundle. In dog 4, the pathologic change was considerable in the approaches to the AV node, the AV node, and the His bundle and bundle branches (Fig. 4), but there was no interruption in continuity of structures. In dog 5, the injury to the AV node (Fig. 5) and His bundle (Fig. 6) were moderate, but marked in the bundle branches (Fig. 7). In dog 6, it was significant in the approaches to the AV node, the AV node itself, less in the His bundle and considerable in the bundle branches but without interruption of the bundle branches.

Discussion

After shocks were delivered through tissue fixation catheters, only minor changes in AV conduction were observed and only with atrial overdrive pacing. In general, dogs that received low-energy shocks (20 to 140 J) showed predominant damage to the AV node and common bundle. Those that received higher-energy shocks (180 to 240 J) showed significant damage of the

FIGURE 6. His bundle in dog 5, showing compression and an infiltration of mononuclear cells. Also seen is degeneration of the subendocardium and connective tissue (CT) on the left of the bundle and young connective tissue (Y) on the right of the bundle. **Arrows** point to AV bundle. V = ventricular septum. Hematoxylin-eosin stain; magnification × 63, reduced 27%.

FIGURE 7. Marked fibrosis of right bundle in dog 5. **Arrows** point to right bundle. B = AV bundle; V = ventricular septum. Weigert-van Gieson stain; magnification × 63, reduced 27%.

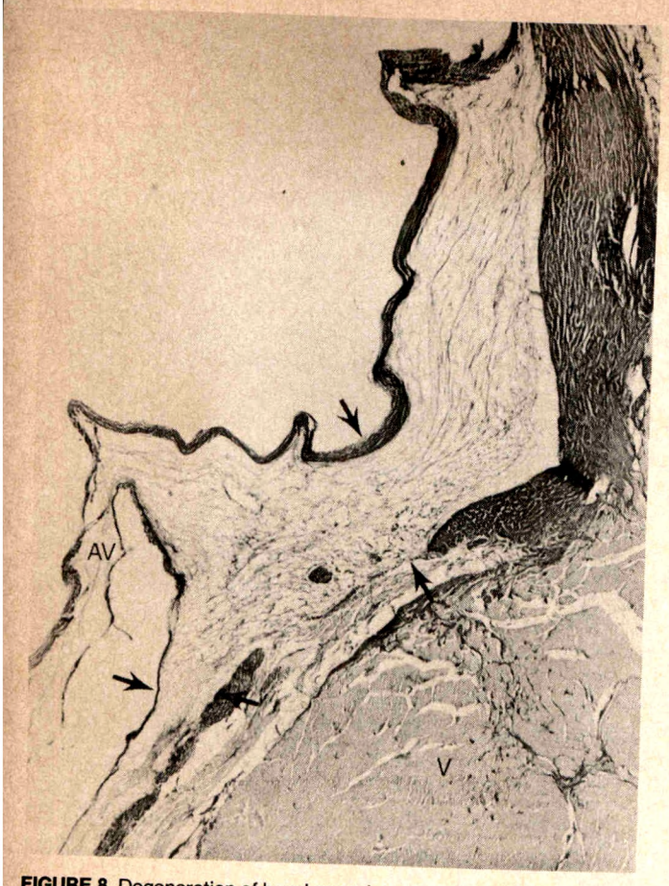

FIGURE 8. Degeneration of basal spongiosa or aortic valve (AV) in dog 2. **Arrows** point to basal spongiosa. V = ventricular septum. Weigert-van Gieson stain; magnification × 45, reduced 28%.

node, common bundle and bundle branches. Complete interruption of the conduction system was not observed. Other findings included degenerative changes in the central fibrous body and summit of the ventricular septum as well as changes in the spongiosa of the tricuspid and aortic valves (Fig. 8). No damage to the epicardial coronary vessels were observed.

Limitations: A potential limitation of this study is the possibility that different doses of sodium pentobarbital (longer duration of anesthesia for the first study) may have affected AV nodal conduction. In addition, the delivered shocks may have altered the autonomic supply to the AV junction and conceivably affected AV nodal conduction. Finally, although more severe histologic damage to the infranodal conduction system was observed in dogs that recieved larger amounts of electrical energy, it is not clear why the predominant electrophysiologic changes were localized to the AV node.

Significance of findings: Although the experiments were designed to deliver localized energy to the region of the AV node, tissue fixation catheters produced significant diffuse damage to multiple areas of the AV conduction system. We show the enormous safety margin of AV conduction, in that dogs with 50% or greater histologic destruction of part of the AV conduction system showed only small functional changes in AV conduction. Whether this degree of damage will allow arrhythmia control in patients with supraventricular tachycardia refractory to medical therapy remains unknown. This technique may allow treatment of these patients without production of complete AV block with permanent pacemaker dependency.

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Mechanical "Cough" Cardiopulmonary Resuscitation During Cardiac Arrest in Dogs

JAMES T. NIEMANN, MD, JOHN P. ROSBOROUGH, PhD, ROBERT A. NISKANEN, MSEE, CLIF ALFERNESS, BSEE, and J. MICHAEL CRILEY, MD

Hemodynamic findings during ventricular fibrillation (VF) and closed-chest cardiopulmonary resuscitation (CPR) are similar to those described during VF and vigorous coughing. Interventions during CPR that mimic the physiologic events of coughing (high intrathoracic pressure and high intraabdominal pressure) improve perfusion during VF and CPR. An external circulatory assist apparatus was devised to emulate cough physiology, i.e., simultaneous pulsatile increases in intrathoracic pressure (pneumatic vest), intraabdominal pressure (abdominal binder) and airway pressure (high-pressure airway inflation). In this study, vest/binder CPR was compared with conventional CPR during 30 minutes of VF and artificial support in 18 randomized dogs. Defibrillation and long-term (more than 24 hours) survival were chosen as end points. During VF and artificial support, aortic and right atrial (RA) pressures, the instantaneous aortic-RA pressure difference (coronary perfusion pressure) and blood gas levels were measured. After 30 minutes of VF and administration of 1 mg of epinephrine, countershock was attempted. Systolic aortic and RA pressures, mean aortic-RA pressure difference and blood gas levels were not significantly different between dogs that were successfully resuscitated and those that were not. However, peak diastolic coronary perfusion pressure (peak diastolic aortic-RA pressure) for survivors averaged 23 ± 6 mm Hg, but only 6 ± 10 mm Hg for nonsurvivors ($p < 0.001$). A peak diastolic coronary perfusion pressure 16 mm Hg or greater had a positive and negative predictive value for a successful outcome of 1.00. Only 1 of 9 conventional CPR dogs survived 24 hours; 7 of 9 dogs supported with the vest/binder device were alive and neurologically normal at 24 hours ($p = 0.007$). Thus resuscitation techniques that exploit the CPR "thoracic pump" can sustain systemic perfusion during VF, and diastolic coronary perfusion pressure is a determinant of CPR/countershock outcome and is favorably manipulated by mechanical means.

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Vigorous coughing during circulatory collapse produces arterial pressure pulses and cardiac output.[1,2] Hemodynamic findings during ventricular fibrillation (VF) and conventional closed-chest cardiopulmonary resuscitation (CPR) are similar to those described during cardiac arrest and so-called cough CPR.[3,4] In an animal model, single coughs, produced by electrical stimulation of the cervical vagosympathetic trunks, generate greater carotid arterial flow than CPR systoles.[5] Newer, experimental CPR techniques[6–8] have incorporated adaptations (abdominal binding with or without simultaneous chest compression and lung ventilation) that mimic the physiologic events of vigorous cough, i.e., pulsatile, simultaneous increase in intrathoracic and intraabdominal pressure of brief duration.

The potential use of cough CPR as an artificial circulatory support technique has been limited to selected settings.[1,2] Although capable of maintaining vital organ perfusion during circulatory collapse, the technique cannot be used for prolonged arrest because of fatigue. However, the use of conventional closed-chest CPR may also be limited during prolonged arrest. Several studies indicate that the absence of a substantial pressure difference between the aorta and right atrium during conventional CPR may preclude effective coronary perfusion and successful cardiac resuscitation.[9–11] In this investigation, CPR performed with a pneumatic device, designed to emulate the physiologic events of spontaneous cough, was studied and compared with

From the Departments of Emergency Medicine, Medicine, and Radiology, UCLA School of Medicine, Harbor-UCLA Medical Center, Torrance, California, and the Department of Physiology, Baylor College of Medicine, Houston, Texas. This study was supported in part by Investigative Group Award 4421G11 from the American Heart Association, Greater Los Angeles Affiliate, Los Angeles, California, and a grant from Physio-Control Corporation, Redmond, Washington. Manuscript received May 25, 1984; revised manuscript received and accepted August 20, 1984.

Address for reprints: James T. Niemann, MD, Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, California 90509.

TABLE I Control Hemodynamic and Arterial Blood Gas Values

	Heart Rate	Aortic Syst	Aortic Diast	Aortic Mean	RA Mean	PaO_2	$PaCO_2$	pH
CCPR (n = 9)	147 ± 13	119 ± 22	98 ± 18	109 ± 19	0 ± 3	526 ± 97	26 ± 9	7.43 ± 0.08
Vest/binder (n = 9)	133 ± 21	119 ± 15	96 ± 13	109 ± 14	2 ± 2	534 ± 103	26 ± 9	7.42 ± 0.10
Group 1* (n = 9)	137 ± 23	121 ± 14	98 ± 12	111 ± 14	2 ± 1	536 ± 84	26 ± 9	7.43 ± 0.09
Group 2† (n = 9)	143 ± 12	117 ± 23	96 ± 18	107 ± 18	1 ± 4	497 ± 102	27 ± 9	7.42 ± 0.09

* Survivors; † nonsurvivors.
Differences between groups were not significant (2-tailed Student *t* test). All values are expressed as mean ± standard deviation.
CCPR = conventional cardiopulmonary resuscitation; Diast = diastolic; RA = right atrial; Syst = systolic.

conventional CPR with respect to countershock outcome and long-term survival after prolonged VF.

Methods

Animal preparation: Eighteen mongrel dogs that weighed 16 to 30 kg were anesthetized with ketamine hydrochloride (10 mg/kg body weight intramuscularly). All dogs were then intubated and anesthesia was maintained with methoxyflurane. During instrumentation, the dogs were mechanically ventilated and heart rate and rhythm were monitored continuously with standard lead II. Transducer-tipped catheters (Millar Mikro-Tip®, size 7Fr with a side hole) were inserted into a femoral artery and vein using a sterile percutaneous sheath technique and advanced into the ascending thoracic aorta and right atrium. Catheter tip position was confirmed either fluoroscopically or by characteristic pressure tracings. Sterile catheters were calibrated in a 0.9% saline bath at 37°C before intravascular insertion. A bipolar pacing catheter was inserted percutaneously into a femoral vein and advanced until the distal electrode was in contact with right ventricular endocardium. Airway pressure was measured with a calibrated Statham P23ID transducer through a side hole in the endotracheal tube connector.

Control intravascular pressures were recorded over a 10-minute period and arterial blood was sampled from the ascending aorta during assisted ventilation with 100% oxygen. Minute ventilation was adjusted or intravenous sodium bicarbonate administered, if needed, to provide an arterial pH of 7.36 or more. Ventricular fibrillation was then induced by passing alternating current through the right heart catheter. Aortic and RA pressures were allowed to stabilize for 30 to 60 seconds before artificial circulatory support was initiated.

Experimental protocols: The dogs were unselected for body weight or chest configuration and were randomized to receive 1 of 2 techniques of artificial circulatory and ventilatory support during VF. Conventional CPR was performed in 9 dogs. Anteroposterior sternal depressions and positive pressure lung inflations with 100% oxygen were administered with a commercially available, cylinder-piston device (Thumper®, Michigan Instruments). The sternum of the supine dogs was depressed 2 to 3½ inches with piston force and depth of compression adjusted to produce an aortic systolic pressure at least 60 mm Hg. Sternal compression was performed at a rate of 60 compression cycles/min. Compression was maintained for 0.5 second (systole) and was followed by a relaxation phase (diastole) of equal duration. A positive pressure lung inflation with a tidal volume of 15 ml/kg was delivered every fifth diastole.

In 9 other dogs, artificial circulatory and ventilatory support was provided with an inflatable, 2-component pneumatic bladder system. The thorax was circumferentially enclosed in an adjustable, snug-fitting vest garment. The abdomen was bound with a circumferential binder that extended from the coastal margins to the midpelvis. The pneumatic bladders of the vest and binder were simultaneously inflated to pressures of 200 and 100 mm Hg, respectively, at a rate of 50 inflations/min. Pneumatic bladder inflation was maintained for 0.6 second (systole) and was followed by a deflation phase (diastole) of equal duration. The lungs were inflated synchronously with vest and binder inflation using a tidal volume of 15 ml/kg for each ventilation.

Artifical circulatory and ventilatory support using conventional CPR or vest/binder CPR was performed during a 30-minute period of VF. Systolic, diastolic and mean aortic and right atrial (RA) pressures were determined every 5 minutes. The instantaneous coronary perfusion pressure (aortic-RA pressure difference) was directly recorded using an electronic subtraction circuit, and systolic, diastolic and mean coronary perfusion pressures were similarly determined at 5-minute intervals. Arterial blood samples were taken from the ascending aorta 10, 20, 25 and 30 minutes after induction of VF and CPR and analyzed for PaO_2, $PaCO_2$ and pH. Sodium bicarbonate (1 mEq/kg) was administered as required to maintain arterial pH above 7.25 during CPR with either technique.

Twenty-five minutes after CPR had been initiated, 1 mg of epinephrine was administered to all dogs through a forelimb vein. Five minutes later, defibrillation was attempted using 100 J. In dogs that underwent conventional CPR, defibrillation was attempted with conventional paddles and conductive gel. In dogs that underwent vest and binder CPR, adhesive, pre-gelled electrodes were used to eliminate the delay in removing the vest before countershock.

If the first attempt to defibrillate at 100 J was successful, sodium bicarbonate was administered as needed to correct metabolic acidemia and an epinephrine drip (2.5 mg in 250 ml of 5% dextrose) was used as necessary to support arterial systolic pressure at a level of 80 mm Hg or greater. When arterial pressure had stabilized and pressors discontinued, intravascular catheters were removed, replaced in a 0.9% saline bath at 37°C, and recalibrated to check for drift. The endotracheal tube was removed when a cough reflex and spontaneous respirations were present, and the dog was observed over the ensuing 24 hours.

If the first defibrillation attempt at 100 J failed, a second shock at 100 J was delivered. If again unsuccessful, defibrillation was attempted up to 5 times at delivered energies of 200, 300 and 400 J. If VF persisted or if asystole, a pulseless idioventricular rhythm or electricomechanical dissociation resulted, CPR with the assigned technique was continued, arterial blood gases were analyzed at 5- to 10-minute intervals, and sodium bicarbonate, epinephrine, atropine and further defibrillation attempts were used according to current guidelines.[12] No dog received conventional antiarrhythmic drugs. If a cardiac rhythm productive of arterial pressure

TABLE II Hemodynamic Data Averaged at 5-Minute Intervals During Artificial Circulatory Support

	Aortic Pressure (mm Hg)			Right Atrial Pressure (mm Hg)			Coronary Perfusion Pressure	
	Syst	End-Diast	Mean	Syst	End-Diast	Mean	Peak Diast	Mean
CCPR (n = 9)	76 ± 12	16 ±10	37 ± 10	73 ± 22	7 ± 4	32 ± 11	8 ± 12	3 ± 10
Vest/binder (n = 9)	152 ± 22*	21 ± 5	63 ± 8*	153 ± 23*	8 ± 3	53 ± 9*	21 ± 7†	8 ± 5
Group 1 (n = 9)	132 ± 36	23 ± 6‡	58 ± 13§	133 ± 36	8 ± 3	48 ± 11	23 ± 6*	9 ± 5
Group 2 (n = 9)	97 ± 44	14 ± 7	42 ± 15	92 ± 46	8 ± 4	38 ± 15	6 ± 10	3 ± 10

* $p < 0.001$; † $p < 0.02$; ‡ $p < 0.01$; § $p < 0.05$ (2-tailed Student *t* test).
Groups 1 and 2 are as defined in Table I.
All values are mean ± standard deviation.
Abbreviations as in Table I.

pulses (with or without pressor support) had not been achieved within 30 mintues of the first attempt at defibrillation, resuscitation was considered to have failed and the experiment was terminated. Transducer-tipped catheters were recalibrated in a 0.9% saline bath at 37°C and drift was recorded.

Data analysis and statistical methods: Peak systolic and mean aortic and RA pressures were measured every 5 minutes using an on-line microcomputer. Mean pressures were derived by computer integration of the respective pressure traces during thoracic compression and relaxation. End-diastolic pressures were directly measured by the investigators. The instantaneous difference between ascending aortic and RA pressures was recorded on a separate channel using an electronic subtraction circuit. On-line computer analysis allowed computation of peak systolic and diastolic differences, as well as the mean difference, obtained by integration of the area of the pressure trace during CPR systole and diastole.

The unpaired Student *t* test (2-tailed) was used to test statistical differences between systolic, end-diastolic, and mean aortic and RA pressures, mean and peak diastolic coronary perfusion pressures, and PaO_2, $PaCO_2$ and pH in dogs that were resuscitated and in those that were not. Fisher's exact test was used to test the null hypothesis that the outcome (24-hour survival) of dogs that received conventional CPR was not different from that of dogs that underwent vest/binder CPR. A p value <0.05 was considered statistically significant.

Results

There was no significant difference in body weight between dogs that received conventional CPR (20 ± 2 kg) and those that received pneumatic circulatory support with the vest and binder apparatus (23 ± 4 kg). Control intravascular pressures and arterial PaO_2, $PaCO_2$ and pH were also similar (Table I). Pressure and blood gas differences between dogs that were subsequently resuscitated (group 1) and those that died (group 2) were not apparent during the control period (Table I).

Intravascular pressures measured at 5-minute intervals during artificial circulatory and ventilatory support are shown in Table II. During the relaxation phase (diastole) of conventional CPR, coronary perfusion pressure (aortic-RA pressure) was positive (aortic pressure greater than RA pressure) in 6 of the 9 dogs that received conventional CPR. A peak diastolic perfusion pressure was seen in these dogs within 200 ms of the onset of relaxation (Fig. 1) and averaged 8 ± 12 mm Hg. During chest compression, coronary perfusion pressure decreased to 0 mm Hg in most dogs. Occasionally, systolic aortic pressure exceeded RA pressure, or the reverse was seen, and a positive or negative perfusion gradient was recorded. This was most often encountered after 15 minutes of chest compression and was believed to be the result of direct cardiac or vascular compression facilitated by changes in thoracic compliance. Mean coronary perfusion pressure averaged only 3 ± 10 mm Hg.

During vest and binder CPR, peak airway pressure ranged from 100 to 120 mm Hg. Systolic and mean aortic and RA pressures were significantly greater than those measured during conventional CPR. Coronary perfusion pressure fluctuations were similar to those seen during conventional CPR (Fig. 2). However, diastolic coronary perfusion pressure was positive in all dogs. A peak diastolic perfusion pressure was seen

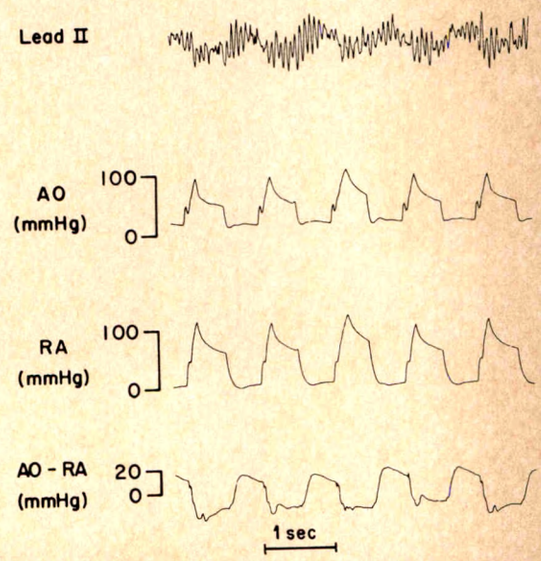

FIGURE 1. Intravascular pressures during ventricular fibrillation and conventional cardiopulmonary resuscitation. Ascending aortic (AO), right atrial (RA) and coronary perfusion (AO-RA) pressures after 25 minutes of ventricular fibrillation and conventional cardiopulmonary resuscitation. A positive pressure-lung inflation was given during the relaxation phase following the second compression in the depicted sequence. The greatest aortic minus right atrial pressure difference occurs during the relaxation phase.

within 300 ms of the onset of relaxation and averaged 21 ± 7 mm Hg ($p < 0.02$ vs conventional CPR) in these dogs during the 30-minute period of VF and artificial circulatory support. Mean coronary perfusion pressure averaged only 8 ± 5 mm Hg and was not significantly different from that measured during conventional CPR.

Nine of the 18 dogs (group 1) were successfully resuscitated after 1 or more countershocks. The cumulative stored energy dose required for successful defibrillation as 738 ± 1,061 J and the average number of defibrillation attempts was 5 ± 6 per dog. The peak current required for defibrillation averaged 27 ± 12 A in the 4 dogs in which it was measured. Four of the group 1 dogs had a peak diastolic coronary perfusion pressure of 25 mm Hg or greater during the 30-minute period of VF and artificial circulatory support. For these dogs, average cumulative energy dose and number of defibrillation attempts were 485 ± 267 J and 3 ± 1, respectively. Seven of the eight 24-hour survivors received vest/binder CPR.

Nine dogs (group 2) were not successfully resuscitated. Only 1 of these dogs had persistent VF after an additional 30 minutes of artificial circulatory support, repeated defibrillation attempts or conventional pharmacologic therapy (excluding antiarrhythmic drugs) for encountered rhythm disturbances. One dog treated with conventional CPR died of hemorrhagic shock 2 hours after successful cardiac resuscitation. The cardiac rhythm most frequently recorded before termination of the experiment in the remaining group 2 dogs was a pulseless idioventricular rhythm (agonal rhythm) (5 dogs). Eight of the group 2 dogs received conventional CPR during VF.

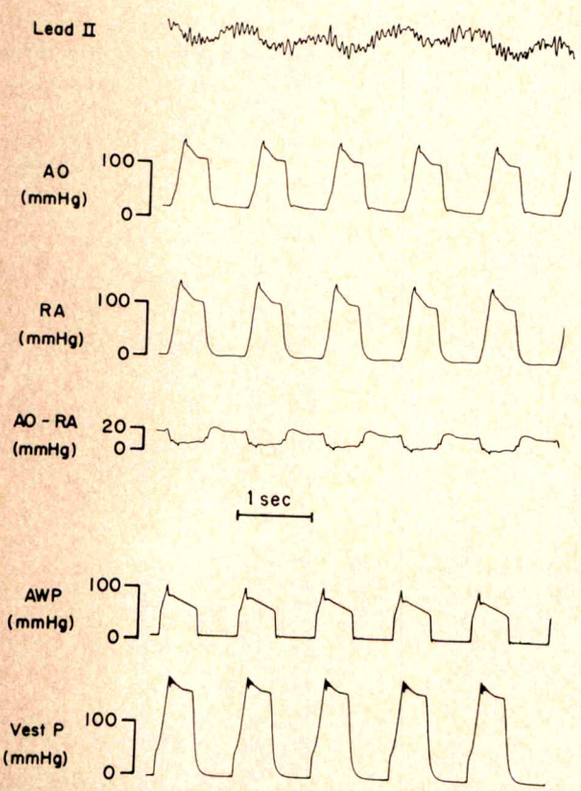

FIGURE 2. Intravascular pressures during ventricular fibrillation and vest and binder circulatory support. Ascending aortic (AO), right atrial (RA) and coronary perfusion (AO-RA) pressures after 25 minutes of ventricular fibrillation and vest/binder cardiopulmonary resuscitation (CPR). Airway pressure (AWP) and vest inflation pressure (Vest P) were also recorded. The vest, abdominal binder and airway were simultaneously inflated during each CPR "systole." The greatest aortic minus right atrial pressure difference is seen after rapid deflation of vest, binder and airway (CPR "diastole").

Hemodynamic and blood gas values for survivors and nonsurvivors are listed in Tables II and III. Successfully resuscitated dogs had significantly greater mean and end-diastolic aortic pressures and peak diastolic coronary perfusion gradients. The integrated mean coronary perfusion pressure was not significantly different between groups. Peak diastolic coronary perfusion pressure measured at 5-minute intervals for the groups are shown in Figure 3. Arterial blood gases were not significantly different between groups.

All successfully defibrillated dogs, except 1, were ambulatory and self-feeding within 24 hours of the experiment. The mean neurologic deficit score for the group was 0.[13] The 1 exception was a dog that received conventional CPR and that died from hemorrhagic shock 2 hours after successful cardiac resuscitation because of multiple liver lacerations. Although successfully defibrillated, resuscitation was considered to have failed in the analysis of the 24-hour outcome.

Only 1 of 9 dogs that underwent conventional CPR during the 30-minute period of VF was successfully defibrillated and survived for 24 hours. Seven of 9 dogs that received artificial circulatory support with the pneumatic vest and binder were defibrillated and survived 24 hours. The survival rate was significantly greater ($p = 0.007$, Fisher's exact test) for dogs that received vest/binder CPR.

Discussion

Artificial coughs produced by the pneumatic thoracic vest and abdominal binder mechanical device resulted in pulsatile systolic intravascular and airway pressure fluctuations of comparable magnitude. Parallel changes in intravascular and intrathoracic/airway pressures have been reported during closed-chest CPR.[3,4] However, mechanical cough CPR arterial pressures were greater than those seen during cardiac arrest and spontaneous cough in patients[1,2] or the electrically stimulated coughs in experimental animals,[5] and were maintained for 30 minutes. In addition, mechanical cough CPR produced greater arterial pressures than those usually reported during circulatory support with simultaneous chest compression and lung ventilation.[6–8]

Long-term survival was significantly different between dogs that received vest/binder circulatory support (7 of 9) and those that received conventional CPR (1 of 9). Successful cardiac resuscitation after prolonged arrest was largely dependent on the magnitude of the CPR peak diastolic aortic-RA pressure difference. A peak diastolic coronary perfusion pressure of 16 mm Hg or greater had a positive predictive value of 1.00 and a negative predictive value of 1.00 for countershock outcome. Dogs with peak diastolic coronary pressures of

TABLE III Arterial Blood Gas Data for Survivors and Nonsurvivors

	Minutes After Induced Ventricular Fibrillation				
	0	10	20	25	30
PaO_2 (mm Hg)					
Group 1	536 ± 84	471 ± 142	546 ± 146	444 ± 183	391 ± 181
Group 2	497 ± 102	317 ± 150	279 ± 151	336 ± 125	318 ± 104
$PaCO_2$ (mm Hg)					
Group 1	26 ± 9	9 ± 5	7 ± 4	10 ± 7	11 ± 6
Group 2	27 ± 9	10 ± 3	9 ± 6	11 ± 7	16 ± 7
pH					
Group 1	7.43 ± 0.09	7.49 ± 0.17	7.40 ± 0.13	7.34 ± 0.08	7.44 ± 0.21
Group 2	7.42 ± 0.09	7.49 ± 0.07	7.33 ± 0.10	7.33 ± 0.14	7.33 ± 0.16

Groups 1 and 2 are as defined in Table I.
All values are mean ± standard deviation.

more than 25 mm Hg required fewer countershocks and less energy for defibrillation than those with perfusion pressures of less than 25 mm Hg.

Our coronary perfusion pressure findings in the intact animal model are in close agreement with, and are supported by, in vitro studies of perfusion pressure requirements of the in vitro fibrillating heart. The fibrillating heart, although incapable of generating systemic perfusion, requires some minimal coronary flow to meet metabolic requirements and, at the same time, may impede coronary perfusion due to intramyocardial compressive forces.[14,15] In the setting of VF and CPR, intrinsic coronary vascular smooth muscle tone is probably at a minimum because of local vasoregulatory responses initiated by myocardial ischemia,[16–18] and intravascular impedance in a nonobstructed coronary vascular bed will be minimal. The in vivo fibrillating canine heart should thus approximate the in vitro fully vasodilated fibrillating heart. If so, resistance to flow will be primarily dependent on the vigor of myocardial contractions (extravascular compressive forces) during VF, and coronary blood flow will be largely determined by the aortic minus RA pressure difference.

In the in vitro model, myocardial perfusion ceases when the aortic-RA gradient falls below 15 to 18 mm Hg.[14,15] In this study, only 1 dog with a peak diastolic perfusion gradient of less than 18 mm Hg, averaged at 5-minute intervals during a 30-minute period of VF and artificial circulatory support, was defibrillated and alive 24 hours later. This dog received conventional CPR and the peak diastolic gradient was 16 mm Hg. No dog with a time-averaged peak diastolic coronary pressure of less than 16 mm Hg was successfully resuscitated.

We measured coronary perfusion pressure rather than coronary flow or myocardial perfusion because (1) electromagnetic flow may be influenced by movement artifacts and the low-flow state that characterizes closed-chest CPR; (2) the radio-labeled microsphere technique may not allow a reliable estimation of myocardial perfusion during CPR if restoration of normal cardiocirculatory function precedes termination of the experiment. A variable number of micropsheres are retained in the left heart blood pool after injection during CPR.[7,8] Redistribution of this pool after restoration of circulation could effect data interpretation; and (3) measurements of coronary flow during CPR in human subjects are not feasible, whereas measurements of aortic and RA pressures are. From a practical viewpoint, successful cardiac resuscitation is the goal of CPR. We attempted to correlate this goal with a quantitative measure which may be obtained in the clinical population. Independent studies by Luce et al,[19] using radiolabeled microspheres, demonstrated a significant correlation (r = 0.66) between peak diastolic coronary perfusion pressure and total myocardial flow. These investigators also reported that myocardial flow during vest/binder artificial circulatory support exceeds that of conventional CPR in the canine model.[7]

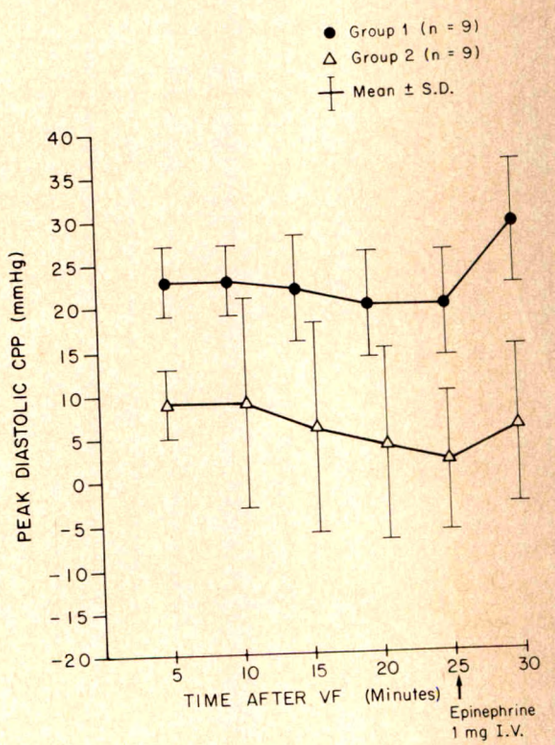

FIGURE 3. Coronary perfusion pressure (CPP) during prolonged cardiopulmonary resuscitation. Diastolic CPPs measured at 5-minute intervals during ventricular fibrillation (VF) and artificial circulatory support are shown. Data points have been slightly offset on the time scale to allow demonstration of standard deviations (S.D.). Epinephrine was given at 25 minutes. Diastolic CPP for successfully resuscitated dogs (group 1) averaged over the 30-minute period was 23 ± 6 mm Hg and was significantly greater ($p < 0.001$) than that measured in dogs that were not successfully defibrillated (group 2, 6 ± 10 mm Hg).

Epinephrine increased coronary perfusion pressure in both resuscitated and nonresuscitated dogs (Fig. 3). Previous investigations have shown that epinephrine increased diastolic aortic pressure and inferred that coronary perfusion pressure was improved.[20–22] However, the perfusion gradient was not measured. The present study supports and confirms this contention by direct measurement of the coronary perfusion gradient. In addition, the reported aortic diastolic pressures associated with successful resuscitation (23 ± 6 mm Hg) are considerably below previously reported values (30 to 40 mm Hg or greater).[11,20–22]

Almost all victims of sudden cardiac death have obstructive atherosclerotic coronary arterial disease.[24,25] Because of this, larger coronary perfusion pressures, greater than those reported in this canine study, may be required during CPR to sustain the metabolic requirements of the fibrillating human heart. Further studies assessing the magnitude of the coronary perfusion gradient and coronary flow during CPR and means by which they may be improved, either mechanically or pharmacologically, are indicated. Resuscitation techniques that exploit the thoracic pump mechanism for systemic perfusion during VF and artificial circulatory support are capable of sustaining vital organ perfusion during cardiac arrest in the most frequently studied model.

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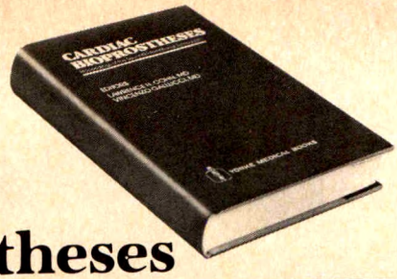

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $69.00

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Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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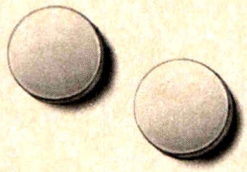

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Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complfications unless properly recognized and managed. Read this section carefully to understand these reactions. With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood. At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients. Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. A paradoxical pressor response has been reported with intravenous use. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Nervous System/Psychiatric:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Paradoxical pressor response with intravenous use. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Digestive:* Nausea, vomiting, distention, constipation, flatus, diarrhea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis, pericarditis. *Skin:* Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis. *Respiratory:* Nasal stuffiness. *Metabolic:* Rise in BUN. *Urogenital:* Breast enlargement, gynecomastia, lactation, amenorrhea, impotence, decreased libido. *Endocrine:* Hyperprolactinemia. *Musculoskeletal:* Mild arthralgia, with or without joint swelling; myalgia.

Note: Initial adult oral dosage should be limited to 500 mg daily in divided doses when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

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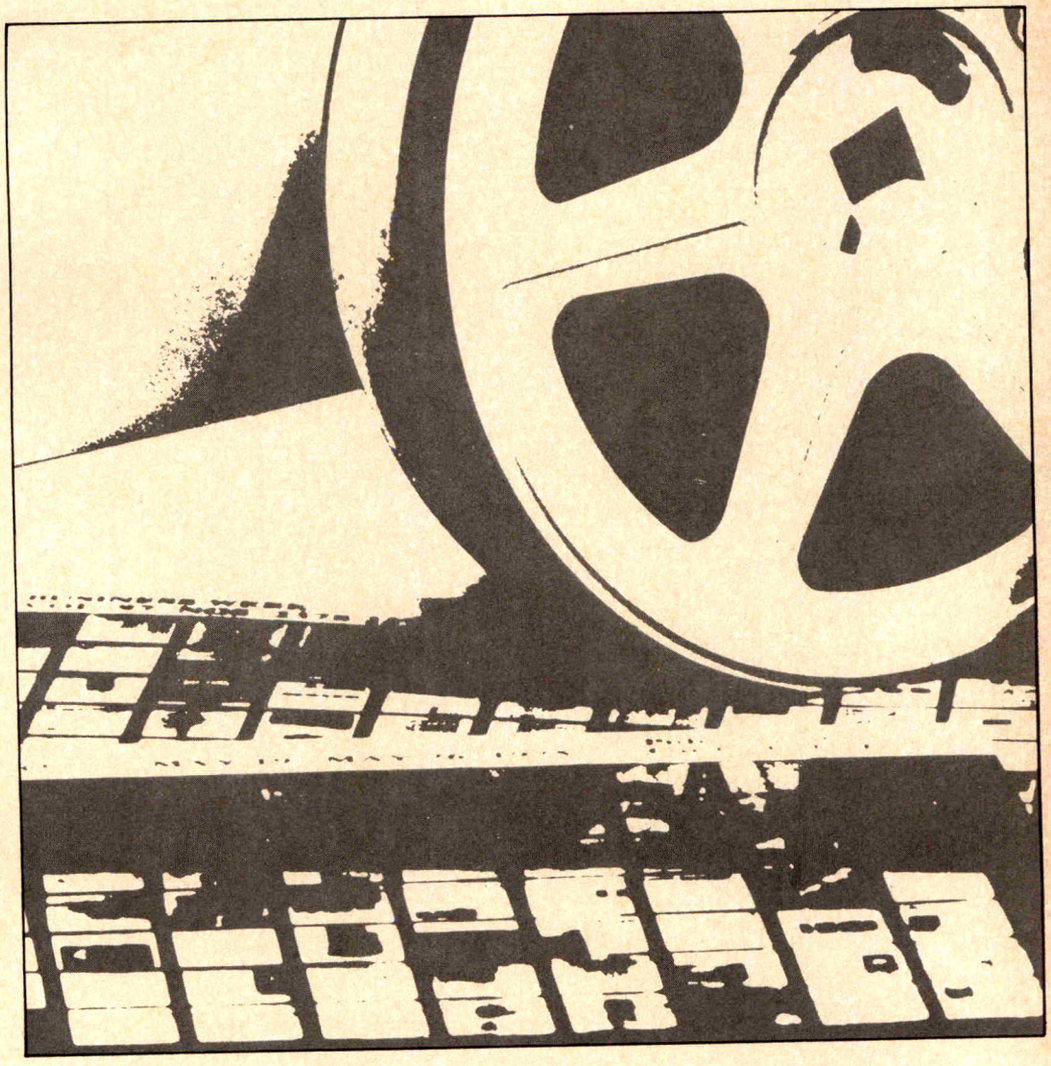

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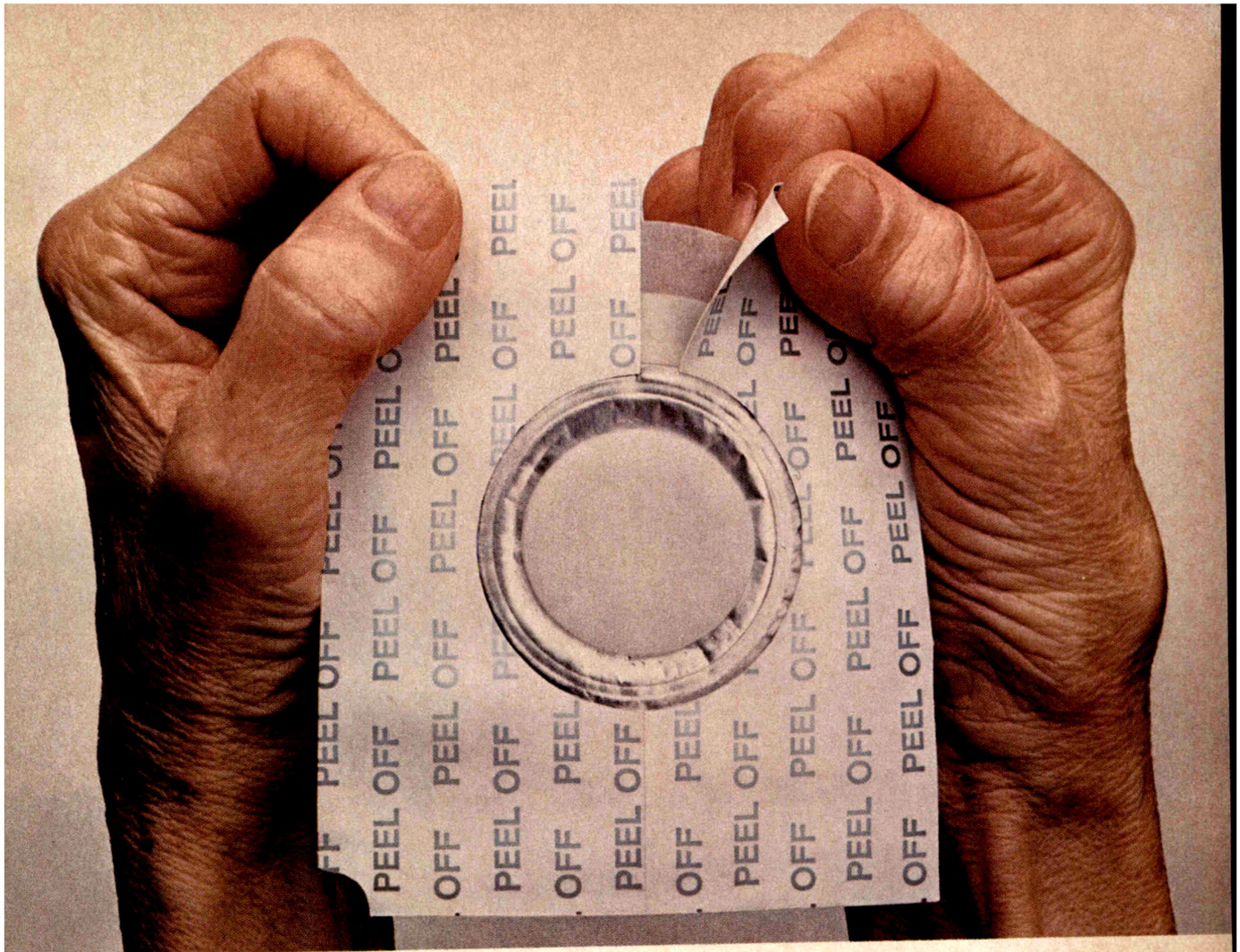

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Symptoms of hypotension may be due to overdosage. If hypotension occurs, the dosage should be reduced. In terminating treatment, the dosage must be gradually reduced over a 4- to 6-week period.

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DESCRIPTION: The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing a range of dosing levels of nitroglycerin. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies using healthy volunteers,[1] transdermal absorption of nitroglycerin from Nitro-Dur achieved steady state venous plasma levels, and maintained these levels for 24 hours. Detectable plasma levels were attained within 30 minutes after application of the system, and were still detectable 30 minutes after removal of the system. Precise definition of "therapeutic plasma level" is not known at this time.

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

Safe use in pregnancy has not been established relative to possible adverse effect on fetal development, but neither have adverse effects on fetal development been established. Therefore, use of nitroglycerin in pregnant women should be balanced against the risk of uncontrolled angina pectoris.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28 and hospital packs of 100.

CAUTION: Federal law prohibits dispensing without prescription.

PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

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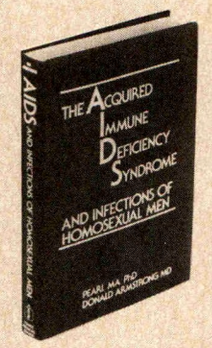

From the Publishers of The American Journal of Medicine, The American Journal of Surgery, and Cutis

Acquire Immune Deficiency Syndrome (AIDS) and Infections of Homosexual Men

edited by **Pearl Ma, PhD,** and **Donald Armstrong, MD** with a foreword by **David J. Sencer, MD,** *Commissioner of Health, New York City; formerly Director, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services*
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The first scientific presentation to review all the facts in full

AIDS has become one of the most publicized diseases in modern times. It has produced fear and confusion in the general public and presented a formidable challenge to the medical community. Physicians and scientists have begun work on managing this epidemic, disease control centers continue to search for answers, and the federal government has declared AIDS the number one health priority of the nation. Understanding this disease demands cooperation between many different medical specialties, and papers on this subject have been published in many diverse journals not regularly read by individual specialists. Now, for the first time, two highly distinguished medical experts, Drs. Pearl Ma and Donald Armstrong, have coordinated in one easily accessible volume the complete range of interdisciplinary approaches to this complex disease, with contributions by the most eminent researchers and physicians in disease control and hospital teaching centers throughout the country. Comprehensive coverage is given to the entire spectrum of sexually transmitted diseases, and an additional section on diagnostic perspectives offers never before published material on why this syndrome occurs primarily among homosexual men. For any physician or other health care professional interested in the prevention and cure of this modern epidemic, this book is an indispensable guide to recognizing and treating AIDS and other sexually transmitted diseases.

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Influence of the Aortic Component of the Second Heart Sound on Left Ventricular Maximal Negative dP/dt in the Dog

DAMON SMITH, BME, and ERNEST CRAIGE, MD

Maximal negative left ventricular dP/dt is widely used as a measure of isovolumic muscular relaxation of the left ventricle. In the course of canine experiments designed to elucidate the hemodynamic events responsible for the aortic component of the second heart sound, high-fidelity left ventricular pressure and dP/dt signals were recorded and accelerations detected on the root of the aorta and epicardium at the cardiac apex. The second heart sound was coincident with maximal negative dP/dt and affected its magnitude to a variable and unpredictable extent. This may account for some of the unexpected variations in magnitude of maximal negative dP/dt that have been described in various disease states and in laboratory experiments where the effects of physiologic and pharmacologic interventions have been studied.

(Am J Cardiol 1985;55:205–209)

The maximal rate of pressure reduction of the left ventricular (LV) pressure signal (maximal negative LV dP/dt) has been extensively used during the past 10 years[1–4] as an index of peak rate of LV relaxation. The determinants of maximal negative LV dP/dt have been studied in animal preparations under controlled conditions. This parameter has been found to vary directly with peak aortic pressure.[2,3] Other factors that have been proposed as having a significant influence are the intrinsic contractility and the end-systolic volume,[1] the rate and extent of fiber shortening during systole[3,5] and the adequacy of coronary perfusion.[6–15]

In patients with both aortic valve stenosis and regurgitation, Eichorn et al[16] found that maximal negative LV dP/dt was not significantly different from that in normal control subjects. This finding was unexpected and occurred although several conditions such as exaggerated peak LV systolic pressure and end-systolic volume index, which increase the maximal negative LV dP/dt, could be shown to be present.

In all the studies cited, the assumption is made that maximal negative LV dP/dt measures exclusively a feature of LV muscular relaxation during isovolumic relaxation. The potential contribution of intracardiac vibrations related to the aortic component of the second heart sound (A_2) was ignored or considered to be insignificant, although the LV dP/dt signal is recorded with a frequency response well into the range of frequencies occupied by the intracardiac A_2 vibration.

In the present report, based on experiments on the open-chest dog, we studied the possibility that the sharp negative spike of the LV dP/dt signal, which is a significant component of the total maximal negative excursion of the LV dP/dt signal at the onset of isovolumic relaxation, is largely an intracardiac pressure transient caused by aortic valve closure.

Methods

Experimental design for study of A_2: During studies concerning the hemodynamic aspects of the second heart sound, 18 mongrel dogs that weighed 20 to 35 kg were anesthetized with intravenous sodium pentobarbital and ventilated by means of a mechanical respirator. The dogs were placed in the supine position and a median sternotomy was performed. The pericardium was opened and sewn so as to create a pericardial cradle for the heart and to allow access to its anterior surface. The proximal aortic root was exposed by blunt dissection to provide clear access to its anterior surface. Aortic and ventricular pressure signals were detected through high-fidelity micromanometer-tipped catheters (Millar Instruments). The aortic catheter was inserted through the right external carotid artery, and positioned within 2 cm of the aortic valve. The ventricular catheter was inserted directly through the LV wall at the apex, and positioned in the apical

From the Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina. This study was supported by Grant 5 R01 HL27459-03 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and the J.P. Riddle Fund of the University of North Carolina Medical Foundation, Chapel Hill, North Carolina. Manuscript received June 15, 1984; revised manuscript received August 16, 1984, accepted August 20, 1984.

Address for reprints: Damon Smith, Division of Cardiology, 338 Burnett Womack Building 229H, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514.

region of the ventricular chamber. The LV pressure signal was passed through an RC differentiation circuit with a time constant of less than 0.2 ms to obtain LV dP/dt. The pressure signals and the LV dP/dt signal were recorded on direct-current input channels of a multichannel physiologic recorder (Electronics for Medicine) with a frequency response bandwidth of 250 Hz. To detect heart and aortic surface dynamics at the time of the A_2 vibration, a miniature accelerometer was used. This accelerometer was of the bonded strain gauge type (Entran Devices), had 1 sensitive axis, and a sensitivity to accelerations at right angles to this of 3% or less of the prime axis sensitivity. The device senses accelerations with a frequency response from 0 to more than 300 Hz. The accelerometer and its associated plastic mounting plate together have a mass of about 1.0 g. The plastic mounting plate has a diameter of approximately 2 cm. We refer to the signal from the accelerometer as "SAA" and label it as such in the figures. The acceleration signal was recorded on the multichannel recorder with a frequency response from 1 to 250 Hz. The accelerometer instrument has been described previously.[17,18] In all 18 dogs, the accelerometer was attached to the anterior epicardial surface, near the apex, using cyanoacrylate glue. The sensitive axis was oriented perpendicular to the epicardial surface, so that inward and outward acceleration transients of the heart surface could be studied. The polarity of the acceleration signal from the apex position was recorded so that an upward excursion of the signal above the baseline was representative of an outward acceleration of the epicardium. In 5 of the 18 dogs, a second accelerometer was attached by cyanoacrylate glue to the anterior surface of the proximal aortic root, within 3 cm of the aortic valve. The sensitive axis of this accelerometer was oriented parallel to the aortic surface, so that accelerations of the aortic wall along the axis of blood flow could be studied. The polarity of the acceleration signal from the aortic surface was such that an upward excursion of the signal above the baseline was indicative of acceleration in the anterograde direction (away from the ventricle), and a negative excursion of the signal below the baseline was representative of retrograde acceleration (toward the ventricle). Thus, in these 5 dogs, a method was provided for the simultaneous analysis of the aortic and ventricular dynamics, in the specified directions, at the time of the A_2.

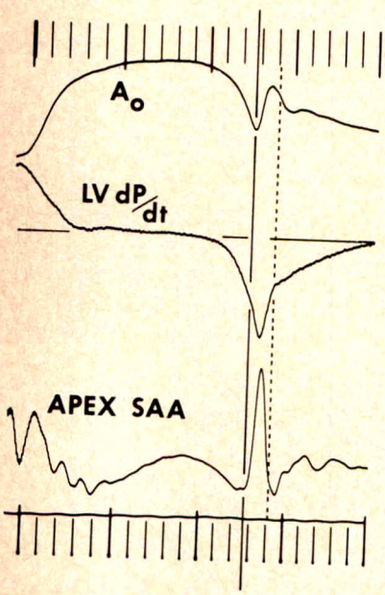

FIGURE 1. Simultaneous detection of the high-fidelity proximal aortic pressure signal (A_o) and the left ventricular (LV) dP/dt signal, along with the acceleration signal obtained at the anterior surface of the LV epicardium near the apex (APEX SAA). The timing of the LV dP/dt signal is accurate to within 0.11 ms for all frequencies. The instant of the incisural notch in the A_o signal is synchronous with the onset of the A_2 acceleration transient at the cardiac apex. The sharp negative spike of the LV dP/dt signal occurs during the time of this A_2 vibration. The termination of this vibration is coincident with a distinct transition in the slope of the LV dP/dt signal, as shown by the **dotted line.** This tracing was recorded at a paper speed of 500 mm/s and the thin lines are 10 ms.

Results

In all 18 dogs studied through the use of the miniature accelerometer, the nadir of the aortic incisura, at the instant of the beginning of the incisural upstroke, was simultaneous with the onset of an abrupt A_2 vibration of the LV epicardial surface near the apex. This vibration has a dominant frequency of approximately 100 Hz, which is consistent with the frequency range of A_2. As seen in the acceleration signal of Figure 1, this A_2 vibration is manifest as an outward acceleration transient of the epicardial surface near the apex. The exact synchrony of the beginning of this acceleration transient with the incisural notch of the aortic pressure signal is shown in the figure, which was recorded at a paper speed of 500 mm/s. The differentiation circuitry used to derive the LV dP/dt signal in this instance was such that the timing of the LV dP/dt signal was accurate to within 0.11 ms for all frequency components. As seen in Figure 1, the sharp negative spike of the LV dP/dt signal occurs during the time of the epicardial A_2 vibration. Furthermore, the termination of the A_2 vibration is associated with a distinct transition in the slope of the LV dP/dt signal, as shown by the dotted line in Figure 1.

In the 5 dogs instrumented with 2 accelerometers, the outward A_2 acceleration transient at the apex was also associated with an abrupt retrograde acceleration transient of the aortic surface, toward the left ventricle, as seen in Figure 2. In beat 2 of this figure, no aortic pressure pulse was produced, and the A_2 acceleration transients at both locations are totally absent.

Occasionally during these studies, the dogs would have pulsus alternans with alternating strong and weak beats. In 5 dogs, we obtained tracings in which some weak beats would exceed aortic pressure and produce an aortic pressure pulse and A_2 vibration, whereas other weak beats of similar or even greater contractile strength would fail to do so. Figures 3 and 4 demonstrate this situation, which allows for an assessment of the contribution of the intracardiac A_2 pressure fluctuation to the LV dP/dt signal. In Figure 3, the first 2 weak beats shown result in attenuated but distinct aortic pressure pulses, and the A2 acceleration transient in the acceleration signal. The sharp negative spike of the LV dP/dt signal that accompanies the A_2 transient is indicated by the arrows in these 2 beats. In the third weak beat of this figure, the LV pressure failed to exceed the aortic pressure and the aortic valve did not open. This is associated with a total absence of the A_2 transient at the apex, as noted in the acceleration signal, and a loss of the sharp negative spike of the LV dP/dt signal. The tracing shown in Figure 4 was recorded from the same dog at a time of increased end-diastolic LV pressure. The weak beats in this instance are stronger than the first 2 weak beats shown in Figure 3, but the weak beats shown in Figure 4 failed to produce the sharp negative

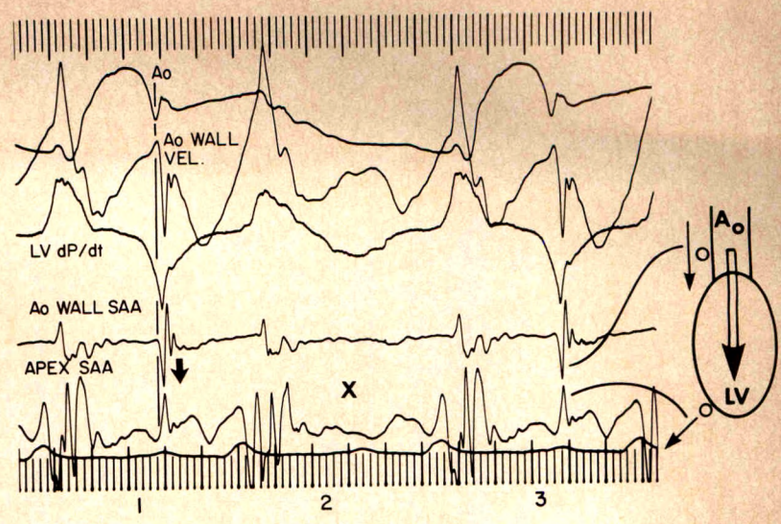

FIGURE 2. Dual accelerometer signals are obtained on the aortic root (A_o Wall SAA) and at the left ventricular (LV) apex (APEX SAA). A velocity (VEL.) signal is derived by electrical integration of the A_o Wall SAA signal, and indicated here as "A_o Wall Vel." The timing and direction of the accelerations at these positions at the time of the A_2 are indicated. At the instant of the A_o incisural notch an abrupt retrograde acceleration of the aortic root occurs and is associated with the acceleration transient observed at the apex. Beat 2 fails to cause an aortic pressure pulse (X) and is devoid of the A_2 accelerations observed in the normal beats. The hypothesized overall A_2 force vector is shown as the **large open arrow.** The **thin time lines** are 10 ms.

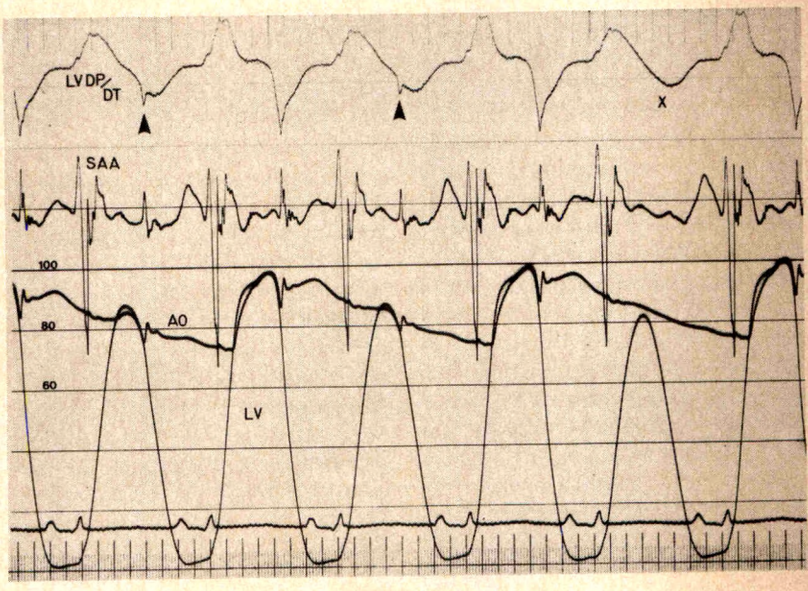

FIGURE 3. A tracing obtained during pulsus alternans in which the weak beats have a variable relation to the aortic pressure (AO). In the first 2 weak beats the left ventricular (LV) systolic pressure exceeds the aortic pressure and causes an aortic pressure pulse and A_2. The sharp negative spike component of the LV dP/dt signal during these beats is indicated by the **arrows.** The third weak beat fails to open the aortic valve. The A_2 vibration is absent in this beat, as shown by the acceleration signal at the apex (SAA). The association LV dP/dt signal is devoid of the sharp negative spike during this beat, as indicated by the X. The electrocardiogram lead II is at the **bottom.** Pressure calibration lines of 60, 80 and 100 mm Hg are shown.

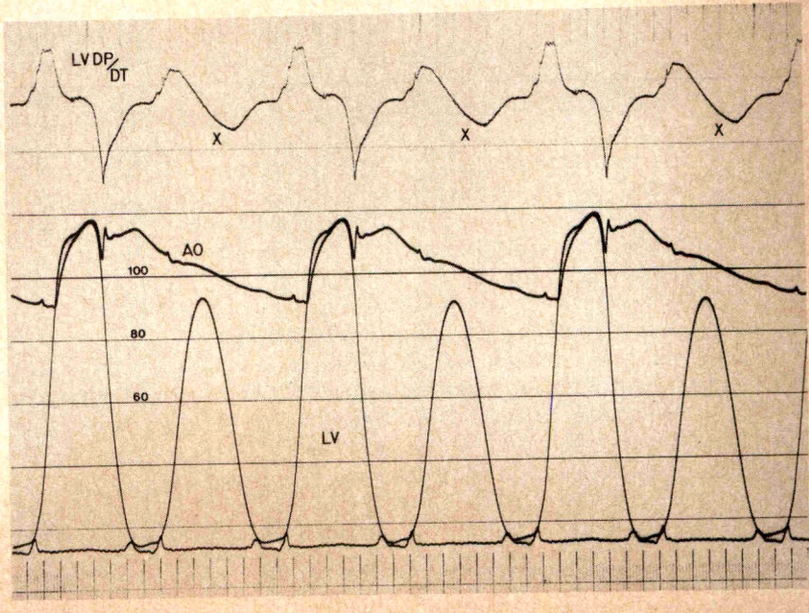

FIGURE 4. A continuation of the study shown in Figure 3, in which the end-diastolic pressure of the left ventricle has increased. The weak beats at this time are stronger than those in Figure 3, but fail to exceed the aortic (AO) pressure and open the aortic valve. As a result, the sharp negative spike component of the left ventricular (LV) dP/dt signal is totally absent as indicated by the X.

spike of the LV dP/dt signal because they did not open the aortic valve and result in an A_2 vibration.

Discussion

Historical perspective: The pioneer studies of Gleason and Braunwald in 1962[19] pointed out the potential use of measurements of dP/dt in assessing ventricular function and the effects of disease processes and pharmacologic interventions. Subsequent investigators have made extensive use of LV dP/dt measurements, initially in investigations of ventricular contraction[20] and, in recent years, ventricular relaxation.[1–4] In a meticulous canine study in 1974, Weisfeldt et al[2] established a close relation between the magnitude of maximal negative LV dP/dt and peak aortic systolic pressure. They were aware of the potential contributions to the dP/dt signal of aortic valve closure pressure transients, but concluded that maximal negative LV dP/dt occurred after the dicrotic notch, so as not to be contaminated by pressure fluctuations of valvular origin. In their subsequent elaboration of the important concept of "time constant T," which provides a measure of the entire time course of isovolumic pressure decrease after achievement of maximal negative LV dP/dt, Weiss, Frederiksen and Weisfeldt[3] noted that this factor does not depend on aortic valve closure. In a later study,[21] the same workers reiterated the observation that aortic valve closure appears to precede maximal negative LV dP/dt. Other investigators have adopted maximal negative LV dP/dt as an accurate measure of the rate of LV muscular relaxation without further concern over the contribution of intracardiac A_2 pressure fluctuations. Their studies have been done to establish the physiologic determinants of maximal negative LV dP/dt and modifying factors, which include inotropic state of the muscle, the volume of the heart at the moment of commencement of relaxation,[1] pharmacologic interventions,[5] coronary perfusion and ischemia.[6–15]

Intracardiac A_2 as studied by high-fidelity micromanometer: The A_2 vibration occurs predominantly in the frequency range of 33 to 111 Hz[22,23] and is manifest on the epicardial surface of the heart,[24] as well as in a pressure transient of the LV intracardiac blood mass.[25] Sabbah and Stein[36] studied the intracardiac A_2, using a micromanometer-tipped catheter inserted from the aorta, and thus passing through the aortic valve. They reported that the intraventricular pressure transient of A_2 was primarily a *pressurization* transient, based on observation of the direction of the vibration on their phonocardiogram. In our attempts to confirm this result, we obtained a signal of an intracardiac *pressurization* transient associated with aortic valve closure only when the distal portion of the manometer-tipped catheter was in obvious contact with the closing leaflets of the aortic valve, causing "hitting" or "catheter whip" artifacts. In our studies, we inserted the catheter directly into the LV chamber through the LV wall at the apex, to avoid the necessity of contact of the catheter with the aortic apparatus. When this was done, we were able to record clear intracardiac A_2 vibrations in the frequency range reported by others. Furthermore, the sharp negative *depressurization* component of the LV dP/dt signal constituted the intracardiac A2 pressure fluctuation, which occurred during the time of the epicardial A2 vibration and had a time period of approximately 10 ms (and, thus, a fundamental frequency of about 100 Hz) (Fig. 1). When we inserted the micromanometer-tipped catheter into the LV chamber from the aorta, with the tip away from the aortic valve, the same result was obtained. The requirement for the sharp negative spike component in the LV dP/dt signal of the weak beats of pulsus alternans is the production of an aortic pressure pulse and the associated A_2 vibration (Fig. 3 and 4). The weak beats of Figure 4 are stronger than those that exhibited the negative spike in Figure 3, but those in Figure 4 did not open the aortic valve and failed to produce the negative spike component.

The overall A_2 mechanism: The simultaneous study of aortic and heart surface dynamics provides insight into the nature of the overall A_2 mechanism. The accelerometer signal is proportional to the net force on the surface to which it is attached, acting along its sensitive axis. The instant of aortic repressurization, which defines the incisural notch, is associated with a distinct force on the aortic root pointing toward the left ventricle (Fig. 2). We believe the only reasonable explanation for the simultaneous appearance of aortic blood pressurization and retrograde force on the aortic root is an abrupt halting of retrograde blood movement by the closed and tensed aortic valve. This gives rise to an overall A_2 force vector, indicated in Figure 2 as the large open arrow. When the flow of fluid within a pipe is abruptly terminated by the sudden presence of a diaphragm instantaneously placed within the moving fluid column, the fluid colliding with the diaphragm causes the "water hammer" effect, producing a sharp pressurization transient within this fluid. Also, the fluid that is "down stream" to the diaphragm transiently pulls against the limiting structure as its momentum is halted, causing a sharp depressurization transient within this fluid. Furthermore, the force of deceleration of this flow, acting on the diaphragm, is transmitted into an overall force acting along the pipe in the direction of the blood flow at the instant of termination of this flow. Sabbah and Stein[27] showed through superb high-speed cinematography, that the flexible aortic valve develops transient but significant retrograde velocity as the valve seats. The pressure fluctuations and force transients that we have observed on and within the aortic and LV chambers are consistent with the concept that the dominant A_2 force arises from abrupt halting of the associated retrograde blood momentum when the valve reaches the limitation of its seating movement.

Temporal relation of A_2 and maximal negative LV dP/dt: The principal basis for ignoring the possible involvement of A_2 in the determination of maximal negative LV dP/dt was the observation that the achievement of the maximal negative excursion of the dP/dt signal occurred after the closure of the aortic valve and the onset of the A_2 vibration.[3] However, our

results show that the nadir of the sharp negative spike of LV dP/dt occurs during the time of the ventricular epicardial A_2 vibration at the apex, and that its timing is consistent with the hypothesis that it is associated with A_2. Perhaps the strongest argument in favor of this hypothesis, in terms of timing considerations, is the abrupt transition in the slope of the LV dP/dt signal that occurs at the termination of the epicardial A_2 vibration (dotted line in Figure 1).

Implications regarding hemodynamic determinants of A_2 intensity: The maximal dP/dt across the aortic valve is correlated with the magnitude of maximal negative LV dP/dt,[28] and has been reported to be the best hemodynamic determinant of A_2 intensity.[28,29] If the sharp negative spike of the LV dP/dt signal is simply the intracardiac manifestation of A_2, the maximal negative LV dP/dt and the maximal dP/dt across the valve are perhaps not *determinant* of A_2 size, but are, instead, largely *dependent* on A_2 size. Our results, and the hypothesis that the A_2 vibration results from the water hammer phenomenon, suggest that the cause-effect relation is reversed as compared with that proposed in these earlier studies.[28,29] Conditions known to be associated with reduced A_2 intensity, such as aortic valve stenosis and incompetence, would have a smaller than expected maximal negative LV dP/dt. We believe that this is the explanation for the finding by Eichorn et al[16] that maximal negative LV dP/dt was smaller than predicted in patients with these conditions. This does not deny the possibility that impaired muscular relaxation results in reduced A_2 intensity, as reported by Stein et al.[28]

Interlaboratory variability of instrumentation: The contribution of the sharp negative spike to the LV dP/dt signal is dependent on the frequency bandwidth of the recorded signal. Lack of standardization of this equipment further complicates the subject of maximal negative LV dP/dt and the involvement of the A_2.

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Morphologic Changes Induced by Dilation of the Pulmonary Valve Anulus with Overlarge Balloons in Normal Newborn Lambs

JOHN C. RING, MD, THOMAS J. KULIK, MD, BARBARA A. BURKE, MD, and JAMES E. LOCK, MD

The optimal method for balloon dilation valvuloplasty of congenital pulmonary valve stenosis has not been established. The cardiac damage produced by using a balloon the same size as the pulmonary anulus has not been described. The use of balloons that are larger than the anulus or of a dynamic dilation technique may enhance gradient reduction, but their added risks are not known. The pulmonary valve anuli of 14 normal newborn lambs were dilated with angioplasty balloons 20% smaller to 90% larger than the anulus; in 3 dilations, a dynamic technique was used, consisting of withdrawal of the fully inflated balloon from the anulus into the body of the right ventricle. Twelve lambs were killed immediately after the procedure and 2 were killed later, and detailed gross anatomic and microscopic observations of the heart were made. These observations support the following conclusions: (1) Dilation of the pulmonary valve anulus with overlarge balloons is "clinically" well tolerated in normal newborn lambs. (2) The major damage to the heart from any balloon is not to the pulmonary anulus, but to the right ventricular outflow tract and free wall, with mural hemorrhages of varying size. (3) Trauma is minor if the balloon is 30% larger than the anulus, but is considerable when the balloon is 50% larger; (4) Trauma is worst subjacent to the proximal end of the balloon, so that longer balloons may cause greater damage; and (5) Resolution of acute right ventricular hemorrhage occurs with small, patchy areas of fibrosis.

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Balloon dilation angioplasty is an invasive, but nonsurgical, technique that has been applied to the treatment of many types of acquired and congenital stenotic lesions in humans.[1–11] Results are often comparable to those after surgery, and the procedure can be safe and cost-effective. Several groups have adapted dilation techniques to the treatment of congenital pulmonary stenosis.[12–16] Gradient relief has, at times, been less than that which results from standard surgical procedures, thus potentially limiting the applicability of this otherwise promising new therapy. Balloons used for balloon dilation valvuloplasty (BDV) have been arbitrarily limited in size to no larger than the pulmonary valve anulus (PVA) itself.[12–15] The cardiac trauma that may result from this procedure has not been described. Dilation technique most often has consisted of static inflation of the balloon across the valve; a dynamic ("Rashkind-type") maneuver has been infrequently used.[16] Our experience with balloon dilation of peripheral pulmonary artery stenosis and coarctation of the aorta in humans and lambs suggests that more complete gradient relief can result from the use of overlarge balloons.[9,10,17,18] What is not known, however, is the largest balloon, relative to the size of the anulus, that can be used without producing an unacceptable degree of cardiac trauma. Therefore, we correlated in the lamb the type and extent of heart injury resulting from BDV of the pulmonary valve with balloon size and dilation technique.

From the Departments of Pediatrics and Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota. This study was supported in part by Grant HL 28241 from the National Institutes of Health, Bethesda, Maryland. Manuscript received April 16, 1984; revised manuscript received August 31, 1984, accepted September 4, 1984.

Address for reprints: James E. Lock, MD, Department of Cardiology, The Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115.

Methods

Normal newborn lambs of either sex, aged 3 to 25 days (mean 12) that weighed 3.5 to 7.8 kg (mean 5.4), were sedated with intramuscular ketamine (2 mg/kg) and restrained. While breathing room air spontaneously a No. 6Fr angiocatheter was placed percutaneously in the right ventricular (RV) outflow tract. Iodinated contrast material, 2 mg/kg, was injected over

1 second and a single-frame lateral right ventriculogram was obtained. The diameter of the PVA was measured directly from the angiogram at the base of the sinuses of Valsalva (Fig. 1) and corrected for magnification using a radiopaque marker of known diameter. Then we placed a 0.032-inch Teflon-coated guidewire far distally in a branch pulmonary artery. A dilation catheter (Meditech) was then advanced over the guidewire until the balloon was centered in the PVA. In 11 lambs, the balloon was inflated in situ with dilute contrast material to a pressure of 5 to 6 atm for 10 seconds, then rapidly deflated; in 3 lambs, static inflation was followed by a dynamic maneuver, in which the inflated balloon was drawn briskly back 1 to 2 cm into the body of the right ventricle before dilation. Dilation balloons, mounted on 8Fr semiflexible catheters, were made of polyethylene, were 3 to 4 cm long, had a maximal inflated diameter of 15 or 20 mm, and were 20% smaller to 90% larger than the PVA when fully inflated. After dilation, a second right ventriculogram was injected to determine any change in anulus size and to look for extravasation of contrast material and tricuspid valve insufficiency.

Twelve lambs were killed, electively, 20 to 30 minutes after dilation, and 2 were killed late (83 and 111 days) after the procedure. The pathologist's examination, performed without knowledge of balloon size or dilation technique, included a detailed description of the gross anatomy, with particular emphasis on the right side of the heart. Tissue sections were taken for light microscopy from the right atrium/atrioventricular node, tricuspid valve, RV free wall and outflow tract, pulmonary valve, and pulmonary artery, and stained with hematoxylin-eosin. Statistical analysis of the data was not performed.

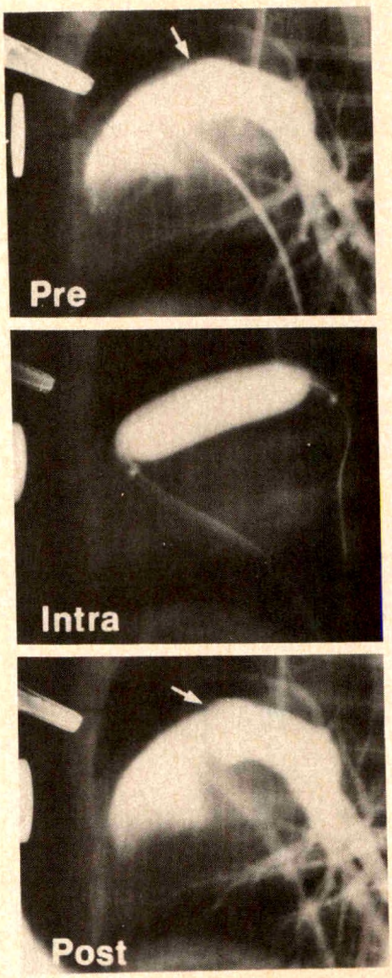

FIGURE 1. Lateral right ventriculograms. **Top,** before dilation. **Middle,** during dilation, with the balloon centered in the pulmonary valve anulus. **Bottom,** after dilation. The **arrows** denote the level at which the anulus diameter was measured.

TABLE I Change in Pulmonary Valve Anulus Size After Dilation with Overlarge Balloons

Lamb	% Balloon Diameter ≥ Pulmonary Valve Anulus	Dilation Technique	% Δ Anulus Size After Dilation
1	−20	S*	0
2	20	S	+7
3	20	D†	+17
4	30	S	+3
5	40	S	0
6	40	S	0
7	40	D	−10
8	50	S	—
9	50	S	+20
10	50	S	—
11	50	D	+16
12	70	S	+13
13	70	S	−5
14	90	S	+68

* Static dilation; † dynamic dilation.

Results

Balloon dilation acutely occluded the RV outflow. Although some degree of systemic hypotension, bradycardia, ventricular ectopy, and restlessness of the animal ensued, none of the lambs required respiratory or hemodynamic support. Similar findings have been reported in dogs[19] and in children,[13,15] even though balloons smaller than the size of the anulus were used. Both of the lambs killed late grew normally and neither had late evidence of hemodynamic compromise.

Follow-up angiography did not show tricuspid insufficiency or extravasation of contrast material. Table I relates the change between the angiographically determined pre- and postdilation PVA size to balloon size and dilation technique. In general, little change in PVA size occurred, regardless of the size of the balloon used or the dilation technique.

The degree of cardiac trauma associated with the procedure was directly related to the size of the balloon used and allowed separation of the lambs into 2 groups.

Group 1 included seven lambs dilated with balloons 20% smaller to 40% larger than the size of the PVA. Two dilation procedures were dynamic and 1 lamb in group 1 was killed late. The gross pathologic findings in this group are summarized in Table II. Acutely, dilations with balloons this size produced small, mostly superficial areas of subendocardial hemorrhage largely confined to the RV outflow tract and free wall, subjacent to the proximal end of the dilation balloon (Fig. 2). Even within this group, there was a tendency for balloons more than 30% larger than the size of the anulus to cause more extensive damage. The heart dilated with the balloon slightly smaller than the size of the anulus was

TABLE II Gross Morphologic Changes After Pulmonary Anulus Dilation

Lamb	Balloon Anulus	Right Atrium	Tricuspid Valve	RV Inflow	RV Outflow	RV Free Wall	Pulmonary Valve	Pulmonary Artery
1	0.8	Normal	1 × 1 H	1 × 1 H PM	Normal	4 × 9 shallow H	Normal	Normal
2	1.2	2 × 2 H	Normal	Normal	Normal	20 × 11 shallow H	Normal	Normal
3	1.2†	2 × 2 H	1 × 1 H	5 × 5 H	Normal	20 × 15 shallow H	Normal	Normal
4	1.3	Normal	Normal	Normal	1 × 1 H	Normal	Normal	Normal
5	1.4	Normal	Normal	Normal	Normal	20 × 7 transmural H	Normal	Normal
6*	1.4	Normal	Normal	Normal	Normal	40 × 25 endocardium	Normal	Normal
7	1.4†	Normal	Normal	5 × 5 H PM	30 × 20 H	10 × 6 transmural H	Normal	Normal
8	1.5	1 × 1 H	Normal	Shallow H	Normal	11 × 15 transmural H	H in cusp	Normal
9	1.5	1 × 1 H	Normal	Normal	Diffuse H	35 × 12 transmural H	H in 1 cusp	Normal
10	1.5	Normal	Normal	Normal	Normal	10 × 5 shallow H	Normal	Normal
11	1.5†	Normal	Normal	Diffuse H	Normal	20 × 18 transmural H	Normal	Normal
12	1.7	1 × 1 H	Normal	Normal	1 × 1 H	30 × 15 transmural H	H in 1 cusp	Normal
13*	1.7	Normal	Normal	Normal	Normal	Normal	Normal	Normal
14	1.9	H	Normal	5 × 4 H PM	Ruptured	40 × 20 transmural H	Ruptured	Ruptured

* Sacrificed late.
† Dynamic dilation. All dimensions of hemmorhage (H) are in millimeters.
PM = papillary muscle; RV = right ventricular.

injured as much as those dilated with balloons slightly larger. The pulmonary valve itself and the proximal pulmonary artery were undamaged in all specimens. Minute, superficial hemorrhages were seen in the anterior leaflet of the tricuspid valve in 2 lambs. Small hemorrhages were also noted at the inferior vena cava–right atrial junction in 2 lambs and in the right atrial appendage of a third, presumably related to catheter passage. The dynamic technique was associated with injury to the RV inflow tract not seen with static dilation using balloons of comparable size. Grossly, the heart of the lamb killed late was normal except for a small area of endocardial thickening.

Group 2 includes 7 lambs dilated with balloons 50 to 90% larger than the size of the anulus. One dilation was performed with dynamic technique and 1 lamb was killed late. The gross pathologic findings in these specimens are recorded in Table II. More extensive cardiac trauma was noted in these hearts and, again, the most marked changes were seen in the RV outflow tract and free wall, subjacent to the proximal end of the dilation balloon; other cardiac structures, however, were more likely to be damaged, too. Hearts from 5 of the 6 lambs evaluated acutely showed transmural hemorrhages that, in general, covered a larger area of the RV free wall (Fig. 3). In contrast to the hearts of the lambs in group 1, 5 of the 6 specimens in group 2 evaluated acutely showed hemorrhage in 1 or more cusps of the pulmonary valve; in 2 hearts, hemorrhage induced valve distortion that may have led to pulmonary insufficiency. The tricuspid valve was normal in all the hearts. Small hemorrhages were seen in the right atrium in 4 hearts, including 1 heart in which hemorrhage was near the expected position of the atrioventricular node. Three hearts demonstrated hemorrhage in the RV inflow tract, especially in the papillary muscle of the conus. Cardiac trauma in the specimen dynamically dilated was no greater than that seen in other specimens statically dilated with balloons of the same size. Again, no gross anatomic abnormalities were noted in the heart of the lamb killed late.

The most extensive cardiac trauma occurred in the heart dilated with a balloon nearly twice the size of the anulus. Although hemorrhage was seen in most structures in this heart, the most intimidating finding was

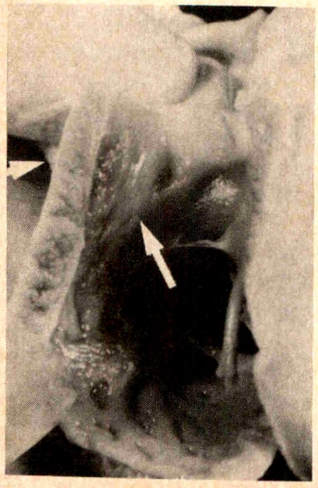

FIGURE 2. Pathologic specimen of a heart in group 1. The right ventricular outflow tract and pulmonary artery are opened, with the base of the heart at the top of the picture. The **arrows** point toward a very small subendocardial hemorrhage in the free wall. The pulmonary valve cusps are normal.

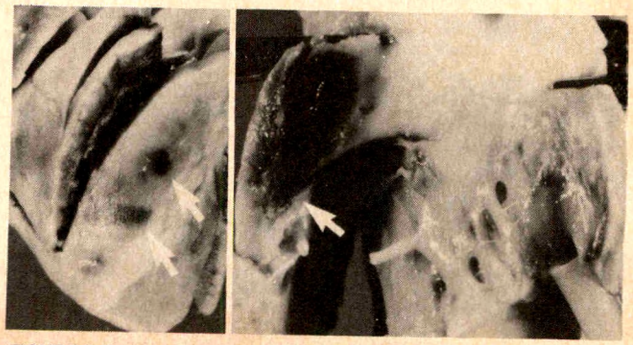

FIGURE 3. Pathologic specimens of hearts in group 2. **Left,** hemorrhage is distributed more widely in the free wall (**arrows**). **Right,** detail of large, transmural hemorrhage in the free wall (**arrow**).

a gaping laceration that extended from the RV outflow tract through the pulmonary valve out to the bifurcation of the pulmonary artery (Fig. 4). Hematoma completely enveloped both great vessels.

Histopathologically, the most marked changes were seen in the RV free wall and outflow tract, then in the pulmonary valve itself. Findings were largely limited to varying degrees of fresh, subendocardial interstitial hemorrhage, though an occasional mural thrombus or focus of endothelial denudation or fibrin deposition was sectioned. Trauma was increased in severity histologically when dilation was performed with larger balloons or dynamic technique. Of interest were small, patchy areas of fibrosis seen in the RV free wall—the area of greatest acute trauma—of both lambs killed late; all other structures in these 2 hearts, however, were normal microscopically. No hemorrhage was found in the atrioventricular node, even in the heart in which, by gross pathologic examination, it was anticipated.

Discussion

BDV may be a safer and more cost-effective mode of therapy than surgery for congenital pulmonary stenosis, but it cannot be considered the treatment of choice unless an equivalent gradient reduction can be achieved and there are no long-term adverse sequelae. Larger dilation balloons and dynamic dilation technique exert more force against the stenotic valve and may, therefore, afford greater gradient relief. These technical modifications, however, may increase the risk of significant, acute cardiac trauma, including tricuspid or pulmonary valve insufficiency, RV dysfunction, uncontrollable hemorrhage in the closed thorax, or frank cardiac rupture.

Clinically, BDV with overlarge balloons is well tolerated by normal newborn lambs. Acutely, there were no signs of sustained low cardiac output and lambs killed late grew normally. These observations mitigate strongly against significant tricuspid or pulmonary valve insufficiency or RV dysfunction being produced by the procedure. They also indicate that the absence of clinical signs of cardiac trauma does not ensure an uninjured heart after dilation.

Pathologically, this study indicates that dilation with balloons up to 30% larger than the size of the anulus is associated with minimal cardiac trauma, while dilation with balloons 50 to 90% larger produces substantial heart injury. Although the data are limited, it appears that no further protection is afforded the heart by using balloons smaller than the size of the anulus. Trauma is largely limited to areas of the right ventricle subjacent to the proximal end of the balloon and appears to be related to the balloon straightening against the curvature of the outflow tract (Fig. 5). Balloons longer than 3 cm, therefore, may cause more extensive injury. Dynamic dilation technique, at least with balloons up to 30% larger than the anulus, may be associated with a greater degree of heart injury, especially in the RV inflow tract. This technique adds somewhat to the risk of the procedure and, if used, should be reserved for stenoses refractory to static dilation.

One late risk of BDV may be resolution with fibrosis of acute hemorrhage in the RV outflow tract and free wall. Other investigators have implicated extensive RV fibrosis as a factor that predisposes patients with repaired tetralogy of Fallot to ventricular dysrhythmias.[20] Though the degree of fibrosis observed in these cardiac specimens was considered less extensive than that seen in human hearts after tetralogy repair, the possibility that BDV may contribute to the genesis of late dysrhythmias cannot be excluded. The probability of late tricuspid insufficiency appears low, but cannot be excluded.

This study has several limitations. Because only single-frame angiograms were obtained, we cannot rule

FIGURE 4. Pathologic specimen of the heart dilated with a balloon 90% larger than the anulus. The **arrow** denotes a through-and-through laceration that extends from the right ventricular outflow tract to the pulmonary artery bifurcation. Hematoma surrounds the great vessels.

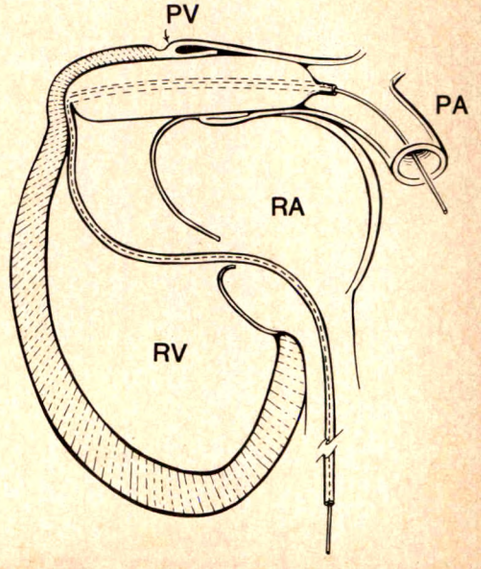

FIGURE 5. A right ventricle (RV) and pulmonary artery (PA) (lateral view), with the dilation balloon superimposed. Note that balloon inflation causes the proximal end of the dilation balloon to distort the curvature of the right ventricular free wall. PV = pulmonary valve; RA = right atrium.

out mild tricuspid insufficiency with confidence. Because only 1 or 2 lambs were studied at any given balloon size, we cannot be too precise in our discussion of balloon limits. The hypertrophied right ventricle may respond to BDV differently than the normal right ventricle and a stenotic pulmonary valve might "protect" the anulus from injury. Nonetheless, we conclude that the use of overlarge balloons—no larger than 30% greater than the size of the anulus—produces a minimal degree of cardiac trauma, and may improve the hemodynamic results of BDV.

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Potential Limitations of Quantitative Thallium Scanning

DAVID M. McCARTHY, MD, and P. TODD MAKLER, Jr., MD

Myocardial perfusion imaging with thallium-201 (Tl-201) has become an accepted technique for evaluating patients with known or suspected coronary artery disease (CAD).[1] This technique is frequently performed in conjunction with exercise stress testing. Perfusion images are obtained immediately after stress and after a 2- to 4-hour redistribution time.[2] The images are examined for the presence of either fixed (scar) or reversible (ischemic) perfusion defects.

When interpreted visually, Tl-201 scintigraphy is reasonably accurate for detecting areas of scar,[3] and is significantly more accurate than stress electrocardiography for diagnosing CAD.[4] However, visual Tl-201 scanning is less accurate for predicting the number of involved vessels[5] or for detecting disease in specific coronary arteries.[6] These are significant limitations, because CAD prognosis relates in part to the extent of disease,[7] and coronary artery bypass grafting may improve survival in subgroups of patients with specific disease patterns.[8] In addition, visual interpretation of Tl-201 scans is often difficult and subject to significant inter- and intraobserver disagreement.[9]

To address some of these shortcomings, some investigators have proposed quantitative methods for analyzing planar Tl-201 scans,[10,11] based on the assumption that the myocardial concentration of the isotope is proportional to local tissue blood flow, and can be determined by the counting rate at the camera face. The initial encouraging reports of quantitative thallium scanning[12,13] have resulted in their widespread clinical use. This review points out some potential limitations of these methods.

Methods of Quantitative Analysis

The principal quantitative techniques are horizontal[10] and circumferential[11] profile analysis. Because the techniques are different they will be described briefly. In both methods, initial image processing involves background subtraction, which is designed to isolate "true" myocardial Tl-201 activity from nonmyocardial scatter. Once the "net" (background-subtracted) myocardial image is obtained the 2 methods diverge. In the *horizontal profile* routine[10] the operator identifies the superior and inferior myocardial walls, and the computer automatically generates horizontal slices at those 2 levels and at 2 evenly spaced levels in between, for a total of 4 horizontal slices that measure the radioactive counts at each specific level. This operation is performed on both the stress and redistribution scans, and the patterns of Tl-201 uptake and washout are assessed against normal established limits.[12]

The other major method of Tl-201 quantification involves the generation of *circumferential profiles*.[11] After background subtraction, the operator marks the center and, in some programs, the apex of the left ventricle; the computer searches radially from the center to the myocardial wall for the peak counts, which are then plotted, usually for sixty 6° sectors to comprise the entire circumference of the heart. Again, this is performed on both the stress and redistribution images, and the results are interpreted according to established criteria.[13]

Either of these methods is at least as accurate as visual analysis for detecting CAD, and significantly more accurate for determining the presence of multivessel disease and lesions in specific coronary arteries.[12,13] In addition, these techniques are assumed to be more reproducible than visual scan interpretation. In fact, we recently studied the reproducibility of circumferential profile analysis,[14] and found that the intraobserver variability (1 observer recalculating profile curves on the same scan) averaged 4.9%, whereas interobserver variability was 5.4%.

Potential Problems with Quantitative Analysis

Quantitative Tl-201 scan analysis is predicated on several assumptions that may not always be true. This can lead to potential problems in interpretation, which will be discussed.

Background subtraction: As noted previously, background subtraction is used in both quantitative methods in order to create a net myocardial image that contains only true heart counts. The subtraction algorithm is generally some modification of the interpolative technique of Goris et al,[15] in which the noncardiac activity in a rectangular region surrounding the heart is used to estimate the noncardiac activity over- and underlying the heart, which is subtracted (pixel by

From the Departments of Medicine (Cardiovascular Section) and Radiology (Nuclear Medicine), University of Pennsylvania School of Medicine, and the Nuclear Cardiology Laboratory, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. Manuscript received June 15, 1984; revised manuscript received August 24, 1984, accepted August 27, 1984.

Address for reprints: David M. McCarthy, MD, Cardiovascular Section, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

pixel) from the heart tissue. This assumption was tested by Narahara et al,[16] who performed Tl-201 scans in dogs before and after removing the heart and replacing it with a balloon that was filled with either water or air. The true background (in the images performed after the heart had been removed) was compared with that estimated by the interpolative approach, and the investigators found that the computer algorithm consistently overestimated the true background activity, which resulted in considerably fewer myocardial counts in the background-subtracted image than were present in the heart scanned in situ. They concluded that caution should be used when subtracting background from Tl-201 images, in particular when there is considerable activity in adjacent organs (e.g., the liver or spleen); in this situation, erroneous regional perfusion defects could result.

Another potential problem with background subtraction occurs when the lung uptake of Tl-201 is increased; this finding is sometimes observed on the stress images in patients with severe CAD, and is probably due to exercise-induced left ventricular dysfunction.[17] Rothendler et al[18] evaluated the potential error in Tl-201 washout caused by increased lung uptake. They simulated increased lung uptake by superimposing technetium-99m-labeled albumin scans on delayed Tl-201 heart images, and compared the net myocardial activity after background subtraction in the same Tl-201 scan with and without the superimposed lung uptake. There was an average 36% increase in myocardial activity in the images without lung activity (due to overestimation of background in the scans with increased "lung uptake"), and the overestimation varied in different regions of the heart, from 18 to 69%. The investigators concluded that this could result in significant errors in calculating regional washout rates of Tl-201. Thus, not only is there the potential for error in the estimation of background, but this error can be compounded in patients with increased lung Tl-201 activity on the images immediately after exercise.

Repositioning variability: Because quantitative Tl-201 analysis is performed on 2 images, 1 immediately after exercise and one 2 to 4 hours later, another potential source of error is the position of the patient relative to the gamma camera. Although standard views are used and the camera head can be adjusted to the same angle, the contribution of variability in repositioning has not been extensively studied. Even when software that allows for apex identification (to correct for rotatory inconsistency) is used the variability of scans performed several hours apart can be substantial.

We evaluated the effect of patient repositioning in 19 patients who had 2 separate redistribution scans performed in the 40° left anterior oblique view.[14] The technologists were instructed to duplicate the position as carefully as possible, and the redistribution scans were chosen for analysis, since there should be little change in Tl-201 activity between 2 scans performed several hours after injection. The 2 scans were analyzed using the circumferential profile method, and there was 12.9% variability in the curves. Even when the variability of reanalysis was taken into account, there was an implicit repositioning variability of 11.5%. Thus, quantitative comparison of 2 scans will have a degree of variability that is independent of the operator or the software.

Level of exercise: Quantitative analysis of exercise and redistribution Tl-201 scans requires that the count profiles and curves be compared with "normal limits" of uptake and washout, values determined in normal patients undergoing Tl-201 imaging. However, patients with CAD often cannot perform the same level of exercise as normal subjects, and the level of myocardial oxygen consumption, coronary blood flow and Tl-201 uptake may be different, not as a consequence of ischemia but because of the different level of stress. Massie et al[19] studied normal subjects on 2 occasions: The first test was a symptom-limited maximal stress test, and the second test was stopped after only one-half of the exercise duration on the maximal test. Thallium-201 exercise and 3-hour redistribution scans were performed in conjunction with both stress tests, and Massie et al found that the washout rate (over 3 hours) was significantly greater on the maximal test than on the submaximal test. In some patients with CAD who exercised submaximally because they reached nonischemic endpoints (e.g., claudication), the washout rates were abnormal in regions *unaffected* by diseased coronary vessels. The investigators concluded that the normal limits of washout, which have been established in normal subjects who have exercised maximally, cannot be used to evaluate Tl-201 washout in patients who exercise submaximally, stopping for nonischemic reasons.

Redistribution kinetics: The observation that Tl-201 activity in the myocardium changes over time has altered the test such that redistribution scans are routinely performed 2 to 4 hours after exercise and are used as the comparison scans for interpretation.[20] This characteristic is 1 of the fundamental principles that has made quantitative analysis feasible, and is used for calculating "washout rates," which are then interpreted for detection of CAD.[12,13] However, patterns of Tl-201 redistribution are variable. Early redistribution of stress-induced defects has been reported both by visual inspection[21] and by quantitative analysis,[22,23] findings that have important implications on when imaging immediately after exercise should commence. However, some defects demonstrate "late" (18 to 24 hours) redistribution; these are generally in regions supplied by severely stenosed coronary arteries, yet with normal wall motion and no evidence for myocardial infarction.[22] Thus, if Tl-201 uptake and washout rates are determined from only 2 scans (i.e., exercise and 2- to 4-hour redistribution), possible errors in assessing tissue viability may result.

Conclusion

Quantitative planar Tl-201 scanning appears to offer advantages over visual scan interpretation, although several factors may affect the results. Although these do not preclude the usefulness of the approach, they should be considered when quantitation is used, espe-

cially in borderline cases or in certain types of patients (e.g., those with increased lung uptake or those who exercise only to submaximal levels because of non-ischemic causes). The newly emerging technique of single-photon emission-computed tomography (SPECT)[24] can also be analyzed quantitatively.[25] Potential problems with background subtraction and excessive lung uptake should be overcome with SPECT imaging; however, SPECT imaging requires specialized equipment that is not yet available in all laboratories. For those using planar quantitation, attention to the limitations should minimize artifactual errors.

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On Pulmonary Vascular Resistance: The Need For More Precise Definition

MAURICE McGREGOR, MD, and ALLAN SNIDERMAN, MD

The term vascular resistance describes, in part, the forces opposing the flow of blood across a vascular bed. It is well recognized that a change of resistance does not necessarily indicate vasomotion. It is less well recognized, however, that resistance as commonly calculated can *appear* to change without any change taking place in any of the forces opposing flow. Since this is a pure artifact of the calculation, it is important that it be understood.

From the McGill University Clinic and the Cardiovascular Research Unit, Royal Victoria Hospital, Montreal, Quebec, Canada.

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Address for reprints: Allan Sniderman, MD, Cardiovascular Research Unit, Room M4.14, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec H3A 1A1, Canada.

Conceptually vascular resistance is comparable to electrical resistance as defined by Ohm's law. The resistance offered by a conductor to the flow of current is a constant, expressed by the voltage drop over any defined distance for any current flow. The resistance of a hydraulic system can be similarly expressed as the ratio of the pressure drop from some upstream point to a downstream point divided by the flow. For fully developed steady flow in a system of smooth walled, regular, nondistensible tubes in which flow is laminar, resistance to flow will be constant and the plot relating change in pressure to change in flow will be a straight line, the slope of which defines the resistance. A shallow slope will indicate a low resistance and a steep slope will indicate a high resistance (Fig. 1a). The ratio of pressure to flow will be constant over a wide range of flows and

can reasonably be referred to under these circumstances as the "resistance" of the system.

In a system in which, instead of being rigid, the vessels which offer resistance to flow are compliant, volume and radius will increase with increasing pressure. Thus, resistance will decrease as pressure increases and the pressure:flow plot will be curved with a diminishing steepness at increasing flows. The resistance will no longer be constant and the flow:resistance plot will reflect progressively lower resistances at higher levels of flow (Fig. 1a). Similarly, if rising pressures cause sequential opening of new parallel vascular pathways (recruitment), resistance will also fall as flow increases.

The pulmonary vasculature is widely considered to behave in this way. As expressed by a contemporary textbook, "as flow increases, pulmonary vascular resistance (PVR) decreases. Consequently, irrespective of whether distention or recruitment occurs, both mechanisms subserve the necessity of maintaining a low pressure circuit during situations of increased blood flow."[1] This description of the pulmonary vasculature, however, is only partly correct and is largely based on erroneous interpretation of experimental data.

There are, of course, published pressure:flow curves that display alinearity, particularly at the lower range, as pulmonary flow is lowered from low normal to 0.[2] However, over the operating range of pressure and flow the evidence indicates that, at least in the dog lung, the slope is either constant,[3,4] or only slightly curvilinear.[2] Thus, resistance is virtually constant, and a decreasing resistance cannot be invoked to explain the absence of pulmonary hypertension at high flows in the normal lung.

The belief that the absence of pulmonary hypertension at high flows is due to recruitment or dilatation of resistance vessels is largely the result of ignoring the existence of a significant "critical closing pressure" in the lung. That is to say, with progressive reduction of pulmonary arterial (PA) pressure, blood flow may cease while PA pressure is still higher than left atrial (LA) pressure. This may be a result of the forces on the outside of the vessels, such as the alveolar pressure on the pulmonary capillaries in zone 2 of the normal lung,[5] or due to elastic or muscular recoil of the vessel wall itself, as occurs in some forms of pulmonary hypertension. Whatever the cause, some pressure is necessary to open the vessels in order for blood to flow, and this has been called the critical opening or closing pressure, or simply the critical pressure.[6]

In a system in which there is a constant resistance and a critical pressure of, say, 10 mm Hg, the pressure-flow plot will intercept the pressure axis at 10 (Fig. 1b). The "resistance" of such a circuit must, as pointed out by Permutt, Bromberger-Barnea and Bane,[7] then be calculated by dividing flow, not into PA pressure nor into the difference between PA and LA pressure, but into the difference between PA pressure and critical pressure, since this is the effective downstream pressure of the system.

If the critical pressure is unknown or ignored and flow is divided into the difference between PA and LA pressure an interesting error is introduced. The pressure:flow plot will still be linear, indicating the absence of any change in true resistance as flow increases (Fig. 1b). The calculated pressure:flow ratio will, however, decrease as the flow increases (Fig. 1b).

Failure to understand this has led to erroneous conclusions about the nature of the pulmonary bed. An example is the study of Borst et al,[3] a diagram of which is reproduced in Figure 2. This diagram shows the relation between PA pressure and flow in the left lung of an anesthetized, open-chest dog ventilated with an end-expiratory pressure of 3.7 mm Hg. The pressure-flow plot is almost linear, indicating that resistance to flow was virtually constant throughout the range of pressures and flows studied. However, in calculating values for resistance, a critical pressure of approximately 12 mm Hg was ignored and PA pressure less LA pressure was divided by flow. In consequence, the ap-

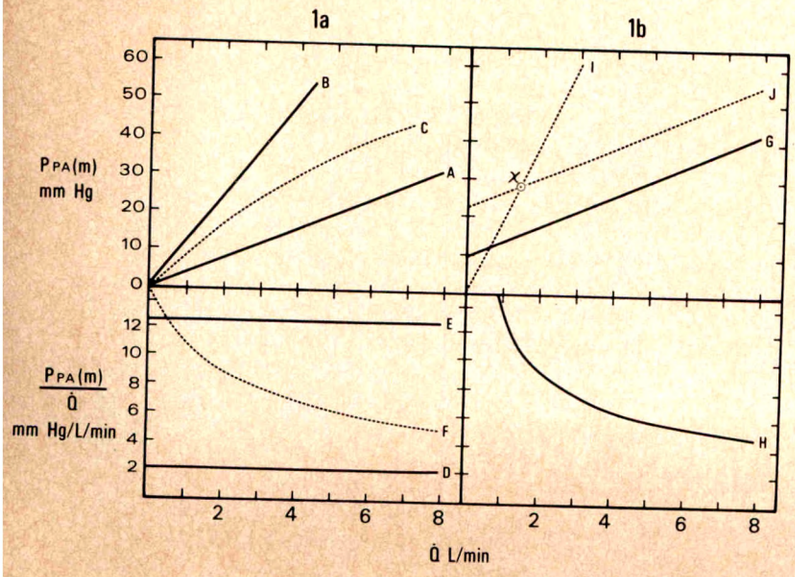

FIGURE 1. Relation between pulmonary flow per lung (Q̇ L/min) and pulmonary artery mean pressure ($P_{PA}(m)$) (**top**) and pulmonary pressure:flow ratio per lung ($P_{PA}(m)/\dot{Q}$) (**bottom**). See text.

parent resistance (the pressure:flow ratio) *appeared* to fall as flow increased, leading Borst et al to conclude, "there was a rapid reduction of resistance as PA pressure increased." It is almost entirely the artifact included in this calculation that has led to the belief that PVR decreases significantly as flow increases. Indeed, there has been much debate as to whether this fall is the result of distention or recruitment of the vascular bed.[8] It is of course the result of neither, but is the consequence of using the incorrect downstream pressure.

In intact man the pressure:flow relations of the normal pulmonary vascular bed are harder to study than in the dog. Consideration of data derived from exercising, supine subjects reported by Bevegard, Holmgren and Jonsson[9] suggests a pressure:flow slope in normal man of about 1.5 mm Hg/liters/min/m^2/min. Unfortunately, exercise introduces other variables, such as changes in LA pressure. These problems can be avoided in the resting supine individual by inflating a balloon so as to obstruct one pulmonary artery. In this way the total cardiac output is directed through the opposite lung. If the assumption is made that flow is divided equally between the 2 lungs and that the intervention causes no disturbance of cardiac output or pulmonary vascular tone, one can use the 2 pressure:flow points obtained before and after balloon inflation to define the resistance of the unoccluded lung over the range in question.[10]

Average points from 6[11] and 4[10] normal persons are shown in Figure 3. Extension of data such as this over a wider range, which can be done by initiating exercise while 1 pulmonary artery remains blocked, suggests that linearity is maintained.[11] Extrapolation from these points to 0 flow suggests an average normal critical pressure of the order of 10 mm Hg. The slope of the pressure-flow plots is about 3.3 mm Hg/liters/min/m^2/lung and the average resistance of the 2 lungs in parallel is thus half this value, or 1.6 mm Hg/liters/min/m^2.

When we consider clinical pulmonary hypertension, it is apparent that with normal LA pressure, raised PA pressure could result either from elevation of critical pressure or from an increase in the true resistance (increased steepness of the pressure:flow plot) or from both. For example, a PA mean pressure of 30 mm Hg and a cardiac index of 3 liters/min/m^2 (or approximately 1.5 liters/min/m^2/lung), point X may be the consequence of a high resistance with a normal critical pressure or of a normal resistance with an elevated critical pressure (Fig. 1b).

Depending on which mechanism is predominant, there will be major differences in the way pressure re-

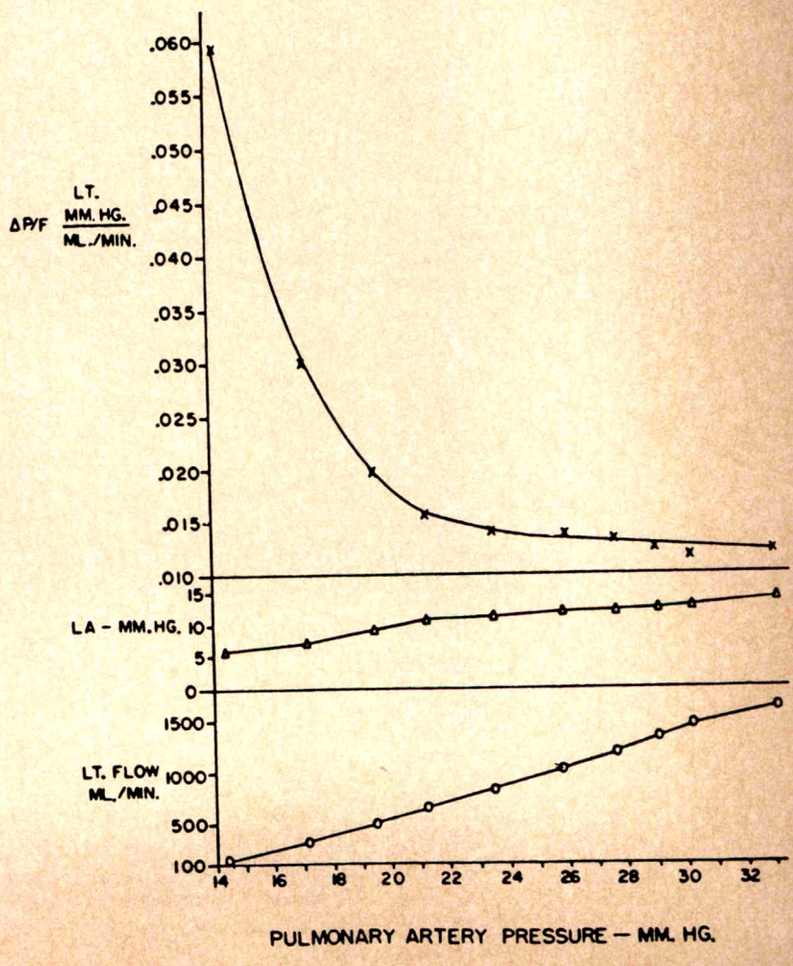

FIGURE 2. Relations between pulmonary artery mean pressure and pulmonary pressure:flow ratio (P/F), left atrial mean pressure (LA) and the flow to the left lung (LT). Flow values are from the study of Borst et al.[3] Increment of pulmonary artery pressure with flow is linear. True resistance is thus constant; but "resistance" as reflected by the pressure:flow ratio falls steeply with increasing pulmonary artery pressure.

sponds to increased output. Thus, if pressures at rest are elevated solely as a result of high critical pressure (Fig. 1b), pulmonary flow could well double without any major increase in pressure. If, however, the pulmonary hypertension were due to an increase in true resistance any increase in flow would be associated with major increments of pressure (Fig. 1b).

The limited clinical data available are consistent with this distinction. For example, average values from 5 patients with pulmonary hypertension due to chronic bronchitis and emphysema and 4 patients with mild to moderate mitral stenosis[11] (Fig. 3) reflect normal resistance with pressure:flow slopes close to normal. High pressures are then the result of high critical pressures. By contrast, when pulmonary hypertension is associated with extensive loss of the vascular bed due to occlusion or fibrosis, one would predict that the true resistance would be elevated. Then, even small increments of flow would cause major increases in the PA pressure. Data obtained from patients with pulmonary fibrosis studied by the Cleveland group are consistent with this hypothesis.[12]

Patients with left heart disease and more severe pulmonary hypertension appear to be intermediate. Data from the studies of Charms, Brofman and Kohn[13] are plotted in Figure 3. Average values are shown for 10 patients with chronic mitral or left ventricular disease chosen for study because cardiac index before and after obstruction of the right or left pulmonary artery varied by less than 500 ml/min/m^2. Pulmonary hypertension here appears to be due both to an increase in true resistance (steep pressure:flow slope) and to elevated critical pressure (44 mm Hg), and is not due to elevation of left heart pressures which averaged 25.6 mm Hg. Calculation of the pressure:flow ratio without knowledge of this critical pressure would not distinguish between these groups. Further, this ratio would fall as flow rose purely as a consequence of the artifact indicated in Figure 1b.

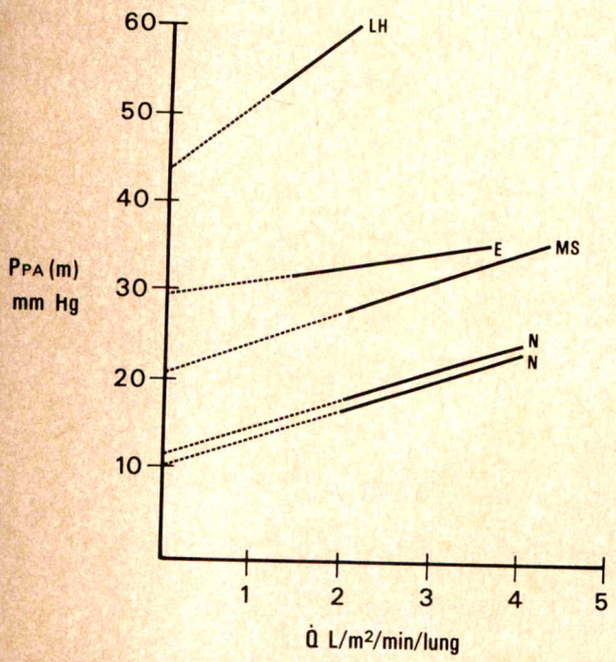

FIGURE 3. Changes of pulmonary artery mean pressure, (P_{PA}(m)) in man before and after flow to 1 lung is increased by obstruction of the opposite pulmonary artery. From data previously reported.[10–13] The **left** and **right** extremity of each **solid line** represents pressure and flow before and after blockage of the opposite pulmonary artery. The **interrupted line** is extrapolated to 0 flow. E = average values from 10 patients with chronic bronchitis and emphysema[11]; LH = average values from 10 patients with left heart disease[12]; MS = average values from 4 patients with mitral stenosis[11]; and N = average values from 6 and 4 normal subjects.[11,10]

Thus, the common practice of calculating so-called resistance using the LA pressure instead of the critical pressure can easily lead to false interpretation of data. In the normal lung, this artifact may be small, but the higher the critical pressure, the greater the artifact produced by ignoring it. In patients with pulmonary hypertension due to lung disease, for example (Fig. 3), this artifact may be extremely large. Here, an intervention which had merely caused a rise in cardiac output would *seem* to have induced vasodilation. Thus, in the absence of knowledge of the slope of the pressure:flow relation, vasodilation can only be concluded to have taken place when a decrease in pressure is observed in the absence of a decrease in flow, or when there is an increase in flow that is not accompanied by an increase in pressure. Failure to recognize this limitation of the pressure:flow ratio can lead to false interpretations in trials of vasodilator drugs in pulmonary hypertension.

In summary, the ratio of PA pressure with or without subtraction of LA pressure, divided by flow, has traditionally been understood to indicate resistance. This is misleading because this ratio will change with changes in flow, without there being any change in the forces opposing flow. To avoid confusion, we suggest that this ratio should be referred to as the pulmonary "pressure:flow ratio." The term PVR should only be used when the correct downstream pressure is known or to describe the slope of the pressure flow plot. PVR, as so defined, is nearly constant over the normal operating range of pressure and flow and does not decrease significantly as pressure and flow increase. The pulmonary circuit can accept high flows without developing high pressures because the resistance of this circuit is low—in normal man, about 1.6 mm Hg/liters/min/m^2.

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Systemic Hypertension, Diuretic Drugs, Arrhythmias and Death

PAUL K. WHELTON, MD, MSc

Epidemiologic studies have repeatedly shown a strong relation between level of blood pressure (BP) and risk of disease and death.[1–3] Risk increases in a curvilinear fashion with progressively higher levels of BP, and there is little evidence of a threshold for BP-related cardiovascular complications. Those with the greatest potential for benefit from antihypertensive therapy are those with BPs in the higher end of the distribution. If therapy is confined to this group of hypertensive patients, however, the burden imposed on society by high BP cannot be substantially reduced.[3] Any meaningful attempt to decrease the number of BP-related complications mandates treatment of the much larger number of persons exposed to only a slight increase in BP and associated risk. Special care to recognize and prevent adverse effects resulting from therapy of such persons is essential.

Given the lifelong nature of antihypertensive treatment and the large percentage of hypertensive patients receiving diuretic drugs,[4] even a slight tendency of thiazides to produce laboratory abnormalities would result in a huge number of patient-years of exposure to the potential risks of such changes. Thus, even a risk that is imperceptible to individual physicians and patients might result in a serious public-health hazard. The reported prevalence of diuretic-induced laboratory abnormalities varies dramatically, depending on the criteria for case definition and the type, duration and dosage of diuretic therapy, the composition of the study group and whether prevalence is being measured at 1 point (point prevalence) or over an interval in time (period prevalence). Whatever the exact prevalence, diuretic-induced biochemical changes such as hypokalemia and lipid/lipoprotein abnormalities are frequent. A variety of electrocardiographic changes also have been reported. For many years it has been known that hypokalemia, if severe, can be accompanied by prominent U waves, ST-T depression, T-wave inversion and ventricular ectopic beats. The results of recent studies that have used exercise and ambulatory monitoring of the electrocardiogram suggest that diuretic-induced ventricular ectopic activity may be a much more common occurrence than was previously recognized. These results, although still controversial, are supported by evidence from both hospital and population-based studies.[5–8]

The proposition that diuretic-induced ventricular ectopic activity may occasionally take the form of ventricular fibrillation and lead to sudden death is controversial, and discussion of information related to this proposal is often emotionally charged. The eagerly awaited Multiple Risk Factor Intervention Trial analyses published in this issue of the Journal provide the most compelling evidence to date of a link between diuretic administration and sudden death.[9] The data presented are substantial and cannot be ignored. Having said that, it is important to recognize the strengths and weaknesses of the information presented. The size of the data base and the care with which the results were collected and analyzed represent major strengths. However, the fact that diuretic-induced sudden death was not a prior hypothesis and that the findings presented are based on subgroup analyses are important weaknesses. As pointed out by the investigators, such analyses do not make use of the randomized trial design. No matter how carefully the analyses have been adjusted, the possibility of confounding by unrecognized factors of importance cannot be excluded. Thus, the reported findings do not and cannot provide conclusive evidence of a relation between diuretic administration and sudden death.

What should the clinician do in view of these new findings? It is relevant that the recorded mortality rate from systemic hypertension, stroke and coronary heart disease in the United States has declined impressively during the same period that diuretic treatment became increasingly common in the community.[3,10] Given this progressive decline in cardiovascular mortality, there is no need for panic and such a response would be in-

From the Outpatient Clinical Research Center, The Johns Hopkins Hospital, Baltimore, Maryland. Manuscript received August 27, 1984, accepted September 4, 1984.

Address for reprints: Paul Whelton, MD, Carnegie 284, The Johns Hopkins Hospital, Baltimore, Maryland 21205.

appropriate. However, caution is in order especially in older men, patients with known electrocardiographic abnormalities, and persons who are concurrently being treated with digitalis. Diuretic drugs should be administered at the smallest dose necessary to achieve the desired reduction in BP.[11] Hypokalemia should be prevented or treated with a salt-restricted diet, potassium-sparing agents or potassium chloride supplements. In addition, alternative forms of drug therapy can be considered. If no contraindications exist, β-blocking drugs provide a well-documented alternative for monotherapy of essential hypertension. In selected instances, monotherapy with a centrally active agent, calcium channel-blocking drug or angiotensin-converting enzyme inhibitor may be more desirable. However, none of the nondiuretic alternatives represents a panacea, because each is known to be a potential cause of undesirable symptoms and laboratory alterations. Moreover, none has been evaluated for the possibility of adverse effects as carefully as diuretic drugs.

The mandate for investigators is more obvious. We need additional information that will confirm or refute the relation between diuretic administration and ventricular ectopic activity. Likewise, clarification of the risk factors and underlying mechanism for any such relation will provide clinicians with a firm basis for prevention and treatment. The hypothesis that a relation exists between diuretic administration and sudden death in certain hypertensive patients with electrocardiographic abnormalities must be explored further. Information from the British Medical Research Council Trial of treatment in mild to moderate hypertension may be informative.[12] Similarly, the ongoing antihypertensive treatment trials of elderly persons may provide valuable information. Unfortunately, the selective nature and sample size of some of these trials may preclude performance of analyses with adequate statistical power. This is not an argument against obtaining the information, but clinicians should be aware that their decisions in this controversial area may have to be based on incomplete data. The best hypothesis test would be provided by a comparison of total and sudden death rates during randomly assigned placebo, diuretic and active nondiuretic treatment of a large group of patients with essential hypertension with and without resting electrocardiographic abnormalities. Unfortunately, financial and practical considerations make the performance of a suitably designed trial of adequate size infeasible.

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Coronary Artery Spasm in Hypothyroidism

WILLIAM E. LAWSON, MD
MARCIS T. SODUMS, MD
LLOYD LENSE, MD
PETER F. COHN, MD

A previous report by Wei et al[1] documented coronary spasm possibly caused by hyperthyroidism. It was speculated that an increase in the number of α receptors secondary to hyperthyroidism may render the coronary arteries more vulnerable to spasm when transient increases in parasympathetic tone with attendant postganglionic catecholamine release occurred. The present report of coronary spasm occurring in a patient with hypothroidism is the first described association of these conditions. The demonstration that spasm may be seen with either hyper- or hypothyroidism suggests that the connection of coronary spasm with thyroid dysfunction may be more tenuous and variable than previously postulated.

A 44-year-old man who drank 1 quart of beer and danced on December 31, 1983, suddenly had severe dull retrosternal and left precordial chest pressure radiating to the left arm with accompanying dyspnea, weakness and vomiting. Examination revealed a systolic systemic blood pressure of 90 mm Hg, and an electrocardiogram (ECG) showed supraventricular tachycardia at 160 beats/min with anterolateral subendocardial ischemia. The patient gave a history of hyperthyroidism treated with radioactive iodine 6 years earlier. He had had no interim symptoms suggestive of either hyper- or hypothyroidism and appeared clinically euthyroid. The patient had no risk factors for atherosclerotic heart disease. In the emergency room the patient responded to treatment with morphine, fluids and dopamine, with conversion to normal sinus rhythm and resolution of hypotension. The repeat ECG was remarkable for minor nonspecific ST-T changes. The patient was given timolol, 10 mg twice a day, and a 5-mg nitroglycerin patch; cardiac catheterization was scheduled. Serial cardiac enzyme measurements revealed a modest, persistent elevation in creatine kinase levels that was noncardiac.

During cardiac catheterization on January 6, 1984, while the left coronary catheter in the aorta was being filled with contrast material, the patient complained of severe angina. The ECG showed transmural inferior wall ischemia (Fig. 1). Immediate infusion of contrast medium into the left coronary artery revealed no obstructive lesions. Treatment with atropine, nitroglycerin and Demerol® lessened the chest pressure within several minutes. Selective coronary angiography, performed within 10 minutes of the onset of chest pressure, revealed normal left and dominant right coronary arteries. The right anterior oblique ventriculogram showed akinesia of the posterobasal and inferior left ventricular wall segments and otherwise normal function. By the end of the catheterization, the ECG had reverted to baseline levels (Fig. 2), and subsequent serial cardiac enzyme levels were normal. Thyroid function tests from admission returned and revealed T_3RIA of 61 (80 to 220 ng/dl), T_4 of 3.6 (5.5 to 11.5 ng/dl) and a TSH of 50 (<9.0 mμ/ml). Timolol administration was discontinued and the patient was given nifedipine and synthroid. There has been no evidence of recurrent coronary artery spasm.

Coronary artery spasm may be mediated both by local factors, such as release of vasoactive prostaglandins and by more generalized disturbances, such as an increase

From the Cardiology Division, Department of Medicine, Room T-17-020, State University of New York Health Sciences Center, Stony Brook, New York 11794. Manuscript received August 6, 1984; revised manuscript received September 4, 1984, accepted September 6, 1984.

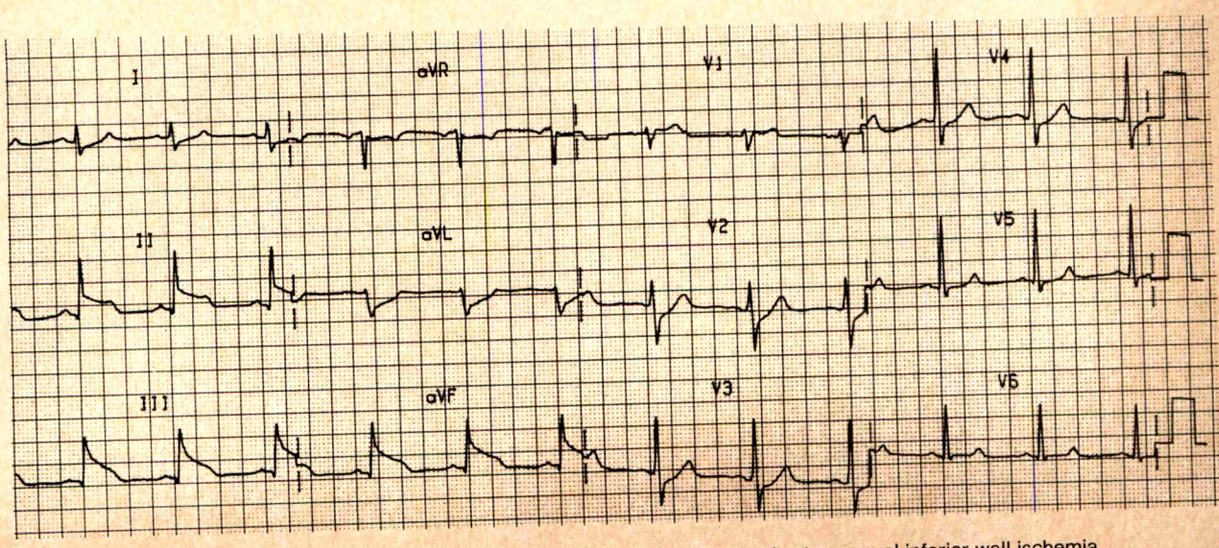

FIGURE 1. Standard 12-lead electrocardiogram during an episode of variant angina showing transmural inferior wall ischemia.

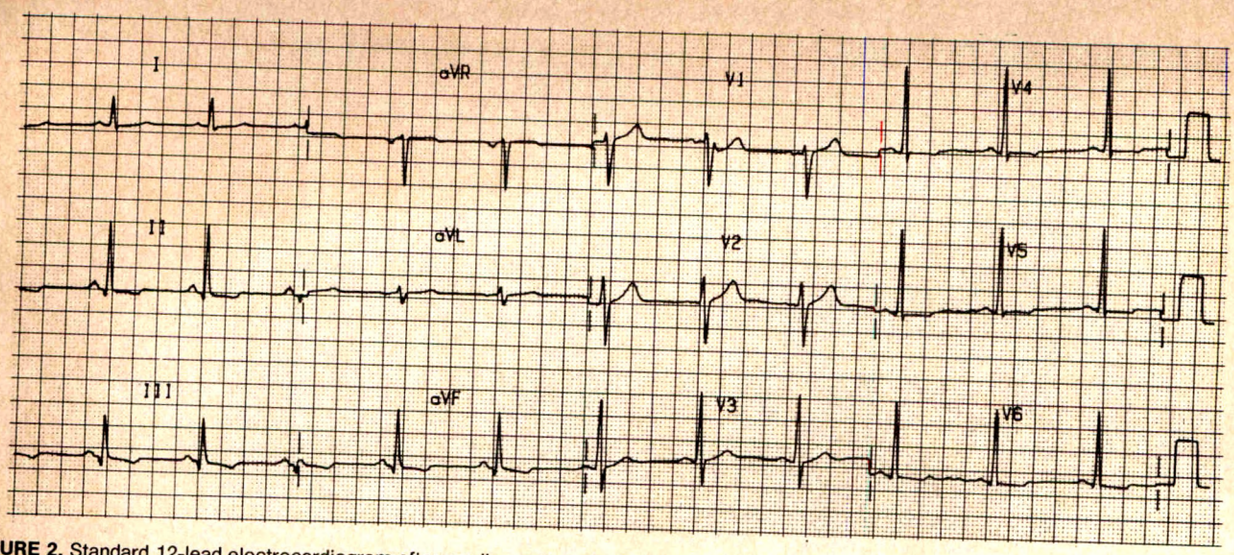

FIGURE 2. Standard 12-lead electrocardiogram after cardiac catheterization.

in circulating catecholamines or autonomic nervous system dysfunction. Advances in our understanding of adrenergic receptor physiology in normal and abnormal states may be applicable to our present case.[2]

An increase in sympathetic nervous system activity or in catecholamine levels results in downregulation with a decrease in β-adrenergic receptor density. Decreased sympathetic activity and low catecholamine levels results in upregulation with an increase in β-receptor density. However, catecholamine levels are not clearly altered with thyroid dysfunction. Beta-adrenergic receptor density increases in hyperthyroidism, which may explain the clinical appearance of increased sympathetic activity. In the hypothyroid patient, both α- and β-adrenergic receptor densities are diminished. The lack of thyroid hormone also affects the coupling of the β receptor with adenylate cyclase causing further functional impairment in the ability to respond to β-adrenergic stimulation. These effects may explain the bradycardia and decreased sympathetic responsiveness seen in hypothyroid patients. In some hypothyroid patients, the lessened ability to respond to β-adrenergic stimulation may render the coronary arteries more susceptible to vasospasm from unopposed α-adrenergic action.

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Thallium-201 Exercise Scintigraphy and Left Bundle Branch Block

SIMON H. BRAAT, MD
PEDRO BRUGADA, MD
FRITS W. BÄR, MD
ANTON P. M. GORGELS, MD
HEIN J. J. WELLENS, MD

Results from several centers have shown that the sensitivity and specificity of exercise thallium-201 (Tl-201) myocardial imaging for detecting myocardial ischemia are superior to those of conventional exercise electrocardiography.[1–6] However, the value of Tl-201 myocardial imaging depends on patient selection, acquisition technique and mode (quantitative interpretation) of images. In patients with normal intraventricular conduction, sensitivity and specificity of Tl-201 exercise myocardial imaging has been reported as 85 to 90%, compared with 65 to 70% for exercise electrocardiography alone.[7] Limited information is available about the value of Tl-201 myocardial imaging in patients with left bundle branch block (LBBB). McGowan et al[8] examined 27 patients with LBBB using potassium-43 or rubidium-81 to exclude coronary artery disease (CAD). Hirzel et al[9] examined 19 patients by Tl-201 scintigraphy and coronary angiography for the same purpose. Both studies found a decreased septal uptake of the radionuclide, suggesting a narrowed left anterior descending coronary artery. However, most patients who had a septal defect had a normal left anterior descending coronary artery by coronary angiography.

From the Department of Cardiology, Annadal Hospital, P.O. Box 1918, 6201 BX Maastricht, The Netherlands. Manuscript received July 25, 1984; revised manuscript received August 31, 1984, accepted September 4, 1984.

To further assess the value of Tl-201 myocardial imaging in patients with LBBB and chest pain and to study its relation to CAD, the present study was undertaken in 24 patients with LBBB admitted to the hospital because of chest pain.

Twenty-four patients (8 women, 16 men), aged 35 to 74 years (mean 54), were studied using Tl-201 stress scintigraphy and coronary arteriography. All patients had chest pains suggestive of CAD. No patient had a history of myocardial infarction.

Thirteen patients had systemic hypertension and 4 patients valvular heart disease: 2 mitral reguritation, 1 patient combined mitral stenosis and regurgitation and 1 mitral and aortic regurgitation. Myocardial imaging using an intravenous bolus of 1.5 mCi of thallium chloride was performed during symptom-limited exercise on a bicycle ergometer and repeated after 4 hours. Scintigrams were obtained in the 45° left anterior oblique, anterior and left lateral projections for 6 minutes using a Philips camera with a parallel-hole, all-purpose collimator interfaced to a Philips minicomputer. Images were acquired at 80 keV with 20% window and recorded with a Polaroid® camera and by computer. Both images were analyzed by 2 independent observers unaware of the coronary artery anatomy. Differences were discussed until consensus was obtained. Coronary arteriography was performed using the Judkins technique. CAD was defined as a stenosis greater than 70%. The angiograms were interpreted by 2 experienced observers and disagreement was resolved by consensus by remeasuring stenoses manually.

In 15 patients at least 1 reversible defect was observed (Table I). In 4 patients the defect was located both in the anterior and inferior walls, in 8 patients, in the inferior wall only, and in 3 patients in the anterior wall only. In 9 patients no defect developed on exercise.

***Coronary arteriography:** Eight patients had no significant stenosis of a coronary artery. Five patients had significant stenoses in all 3 coronary arteries. In 5 patients 2-vessel CAD was found: 3 had left anterior descending and left circumflex narrowing and 2 left anterior descending and right CAD. In 6 patients 1-vessel CAD was present: 4 had right, 1 left anterior descending and 1 left circumflex CAD.*

***Correlation between thallium-201 scintigraphy and coronary arteriography:** In 14 of the 16 patients with at least 1 significant coronary narrowing, a reversible defect was noted on Tl-201 scintigraphy. A false-negative scintigraphic response was found in 2 patients. One had 1-vessel CAD (right coronary artery) and the other had significant narrowing in the left anterior descending and the left circumflex coronary arteries. Among the 8 patients with normal coronary arteries, 1 patient had a reversible defect in the septal area. Sensitivity, specificity and predictive accuracy of Tl-201 scintigraphy in our patients were 88%, 86% and 87%, respectively.*

TABLE I Findings in the 24 Patients

Pt	Tl-201 Defect	Coronary Angiogram	Other Disease
1	Ant + inf	3-vessel	Hyp
2	Ant + inf	R + LAD	Hyp
3	Absent	Normal	Hyp
4	Inf	3-vessel	
5	Inf + ant	3-vessel	MR
6	Absent	Normal	
7	Ant	Normal	
8	Ant	LAD	
9	Absent	Normal	
10	Inf + ant	LAD + LC	Hyp
11	Absent	R	Hyp
12	Absent	Normal	Hyp
13	Ant	LAD + LC	Hyp
14	Inf	3 vessel	Hyp
15	Absent	Normal	
16	Absent	Normal	
17	Absent	LAD + LC	Hyp
18	Inf	R + LAD	Hyp
19	Inf	LC	Hyp
20	Inf	R	Hyp
21	Inf	3-vessel	Hyp
22	Inf	R	MR
23	Inf	R	MR + AR
24	Absent	Normal	MR + MS

Ant = anterior; AR = aortic regurgitation; Hyp = hypertension; inf = inferior; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; MR = mitral regurgitation; MS = mitral stenosis; R = right coronary artery.

The left bundle usually arises as a broad sheet of fibers from the bundle of His to the left side of the muscular ventricular septum, but its anatomy is variable.[10] The anterior half of the left bundle has a dual blood supply in 50% of patients through the atrioventricular (AV) nodal artery from the right coronary artery and from the septal branch from the left anterior descending coronary artery.[11] In 40% of patients, the septal branch is the only blood supply and in 10% the AV nodal artery is the only supply. In 50% of patients the posterior half of the left bundle receives its blood supply from the AV nodal artery. A dual blood supply by the AV nodal and septal branch arteries is present in 40% and in 10% perfusion is by the septal branch alone. Therefore, in a large proportion of patients, the anterior and posterior half of the left bundle has a dual blood supply. Lie et al[12] reported a high incidence of LBBB in patients with inferior wall infarction, suggesting that frequently the mainstem of the left bundle was perfused by the right coronary artery.

Because the left bundle has a dual blood supply in 50% of patients, one would expect 2 defects in these patients, in the septal and in the inferior area on Tl-201 exercise scintigrams, when the cause of the LBBB is ischemic. Two defects were seen in 4 patients. All 4 had significant stenoses in at least 2 coronary arteries. A reversible inferior wall defect alone was seen in 11 patients. They all had at least 1 significant coronary artery narrowing. These observations suggest ischemia as the cause of LBBB in at least 4 patients, although the possibility that the LBBB was caused by systemic hypertension cannot be excluded.

In this study only 1 patient with no significant coronary narrowing showed a reversible septal perfusion defect.

The disparity between the results of our study and that of McGowan et al[8] can be explained by different imaging agents: They used potassium and rubidium-81.

Hirzel et al[9] used Tl-201. Among 19 patients with a history suggestive of CAD, 15 had normal coronary arteries, although all showed a septal defect on Tl-201 scintigraphy. Rowe et al[13] found a defect on Tl-201 scintigraphy in the inferior wall in 2 of 6 patients with CAD and in 4 of 7 patients with normal coronary arteries. They concluded that defects in the inferior wall were seen only in patients with CAD. Our results

also indicated that the area of ischemia in patients with LBBB and CAD was usually located inferoposteriorly.

In 12 of our 15 patients with Tl-201 defects and CAD, the location was inferoposterior, compared with 7 in the anterior area, while 1 of the 3 patients with a single septal defect had normal coronary arteries. Thallium-201 exercise scintigraphy was valuable for detection of CAD in patients with LBBB, who present with angina pectoris. In most patients the area of ischemia is located only inferoposteriorly or is accompanied by a septal defect.

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Effects of Noncaptured Stimuli During Rapid Right Ventricular Pacing: Does Concealed Conduction Occur in the Human Ventricle?

WILLIAM G. STEVENSON, MD
ISAAC WIENER, MD

Concealed conduction was defined by Langendorf[1] as "the effect of a non-propagated impulse upon conduction of a subsequently propagated impulse." Subsequently, examples of concealed conduction have been described occurring in the atrioventricular node, His-Purkinje system and bundle branches.[2,3] In 1978, Sung et al,[4] using rapid atrial pacing, demonstrated concealed conduction of noncaptured stimuli in the human atrium. In an attempt to demonstrate this type of conduction in the human ventricle, we applied Sung's method to 18 patients undergoing electrophysiologic study.

Electrophysiologic studies were performed in the postabsorptive state in the absence of antiarrhythmic drugs. The His bundle electrogram was recorded with a 6Fr tripolar catheter positioned across the tricuspid valve. Pacing was performed using a 6Fr quadripolar catheter with 10-mm interelectrode distances positioned in the right ventricular apex. Three patients also had pacing performed from the right ventricular outflow tract, and 3 patients had left ventricular pacing. Pacing was performed using a Medtronic 5325 stimulator that delivers a 2-ms square-wave impulse. Pacing was performed at twice diastolic threshold. The distal electrode pair was used as the cathode (distal) and anode; a ventricular electrogram was recorded from the proximal electrode pair. Surface electrocardiographic leads I, II and III and bipolar intracardiac electrograms were recorded on an Electronics for Medicine DR-16 multichannel recorder at a paper speed of 100 mm/s and filtered from 30 to 500 Hz. Bursts of ventricular pacing at progressively faster rates were performed until 2:1 ventricular capture occurred. The pacing cycle length was then doubled. The time from stimulus artifact (S) to the ventricular electrogram recorded from the proximal electrodes of the pacing catheter (V_{RV}) and the His catheter (V_{His}) was measured at both pacing rates.

Five patients were studied because of resuscitation from cardiac arrest, 4 because of ventricular tachycardia, 4 because of unexplained syncope, 3 because of atrioventricular block, 1 patient because of atrial tachycardia and 1 because of Wolff-Parkinson-White syndrome. Six patients had coronary artery disease, 2 had dilated cardiomyopathy and 10 had no known structural heart disease.

In the 18 patients and 24 sites studied, 2:1 ventricular capture developed at a mean cycle length of 232 ± 23 ms. The mean S-V_{RV} was 53 ± 17 ms and S-V_{His} was 92 ± 22 ms during 2:1 capture. During 1:1 capture at a mean cycle length of 462 ± 46 ms, the mean S-V_{RV} was 52 ± 17 ms and S-V_{His} was 91 ± 22 ms (difference not significant). In no patient was there more than a 5-ms change in conduction time as measured from S to V_{RV}, S to V_{His} or V_{RV} to V_{His} comparing 2:1 ventricular capture to 1:1 capture. Figure 1 illustrates the findings during 2:1 and 1:1 ventricular capture in 1 patient. There were no arrhythmias induced by pacing at rates with 2:1 capture.

Sung attempted to demonstrate concealed conduction in the atrium by incremental atrial pacing to the point of 2:1 capture and then halving the pacing rate, such that the rate at which the atrium was captured remained constant. The time from stimulus artifact to the recording of the high right atrial electrogram, and from high right atrial electrogram to low right atrial electrogram during 1:1 and 2:1 atrial capture were compared.[4] They showed prolongation of intraatrial

From the UCLA School of Medicine, Center for the Health Sciences 47-12, Division of Cardiology, Los Angeles, California 90024.

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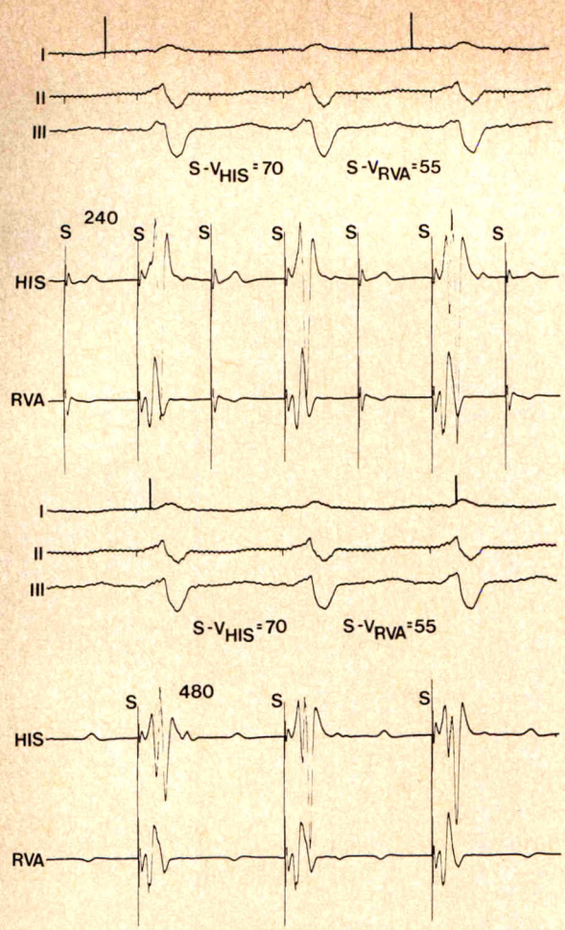

FIGURE 1. Pacing from the right ventricular apex at a cycle length of 240 ms with 2:1 capture (**top**) and 480 ms with 1:1 capture (**bottom**) in the same patient demonstrating no change in S-V_{RV}, S-V_{His} or V_{RV}-V_{His} intervals. Time lines are 1 second.

conduction times of 15 ms or longer during 2:1 atrial capture in 12 of 35 patients. All 12 had evidence of atrial disease manifested as sick sinus syndrome, "chronic conduction system disease," paroxysmal supraventricular tachycardia, or atrial flutter or fibrillation. Sung suggested that during 2:1 atrial capture, the nonpropagated stimulus partially penetrated the atrium (concealed conduction), delaying conduction of the subsequent stimulus.

We could not demonstrate this phenomenon in the human ventricle. We used the same pacing technique, and 2:1 capture occurred over an overlapping range of pacing cycle lengths (200 to 290 ms in the ventricle vs 150 to 260 ms in the atrium). Our failure to demonstrate concealed conduction in the ventricle may relate to differences in the electrophysiologic properties of human atria and ventricles. Sung's patients had a variety of conduction abnormalities or spontaneous atrial arrhythmias. Hordof et al[5] studied atrial fibers from such patients and demonstrated diminished resting potentials and slow action potential upstrokes, features that are associated with slow conduction velocity and calcium dependency. However, these abnormalities, which result in recurrent atrial arrhythmias, may be incompatible with survival when found in the ventricle, and may have been absent in our patients. Moreover, Spach and Kootsey[6] showed that marked slowing of conduction can occur in normal atrial tissue because of impulse propagation perpendicular to the long axis of atrial fibers. This transverse conduction has a greater safety factor than longitudinal conduction and can therefore be seen during premature stimulation.

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Polymorphic Ventricular Tachycardia and Ventricular Fibrillation Due to N-Acetyl Procainamide

JOHN M. HERRE, MD
JAMES A. THOMPSON, MD

Worsening of ventricular arrhythmias has been reported during therapy with class I antiarrhythmic agents.[1] N-acetyl procainamide (NAPA), the first metabolite of procainamide, has been implicated as a cause of polymorphic nonsustained ventricular tachycardia (VT) in 1 patient.[2] Sudden death has occurred during NAPA therapy, but recurrent ventricular fibrillation (VF) resulting from NAPA treatment alone has not been documented previously.[3,4] The following case demonstrates this phenomenon.

A 66-year-old man was admitted to the hospital for elective right hemicolectomy. He had had acute myocardial infarctions at ages 60 and 62 years, but neither angina pectoris nor symptoms of heart failure subsequently. At admission, he was taking quinidine sulfate (1,200 mg/day) for control of ventricular premature complexes (VPCs) and asymptomatic nonsustained ventricular tachycardia (VT). He had been undergoing chronic hemodialysis since age 63 years (1981) because of hypertensive renal failure.

Quinidine treatment was stopped at surgery. On the fifth postoperative day, multiform VPCs and nonsustained VT

From the Cardiology and Pulmonary Divisions, Hunter Holmes McGuire Veterans' Administration Medical Center, 1201 Broad Rock Boulevard, and the Medical College of Virginia, Richmond, Virginia 23249. Manuscript received May 29, 1984; revised manuscript received August 17, 1984, accepted August 20, 1984.

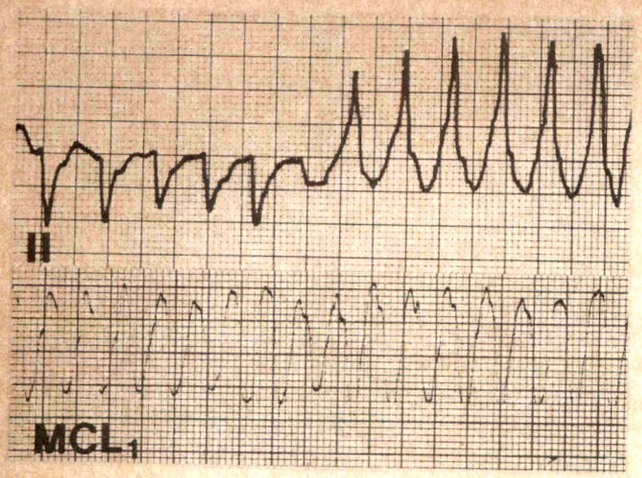

FIGURE 1. Top, polymorphic ventricular tachycardia before discontinuation of procainamide. **Bottom,** recurrent ventricular tachycardia 9 days after procainamide was discontinued (procainamide level <1.0 mg/liter). II = electrocardiographic lead II; MCL = modified clavicular lead I.

(to 5 beats) were noted. Lidocaine was ineffective and intravenous procainamide therapy was begun and the dose was increased to 4 mg/min. On the eleventh postoperative day, the patient had a seizure and was treated with phenytoin. On the twelfth postoperative day, he again had a seizure. The electrocardiogram demonstrated both polymorphic nonsustained VT (Fig. 1) and VF requiring cardioversion. The corrected QT interval after cardioversion was 700 ms. The procainamide level was 21 mg/liter and the NAPA level was 52 mg/liter. Procainamide therapy was discontinued. No other causes for VT/VF were delineated. The left ventricular ejection fraction was 39% by multiple-gated blood pool scan. Polymorphic VT and VF recurred 9 hours later. Atrial pacing was instituted at 110 pulses/min and increased to 140 pulses/min before resulting in complete suppression of the arrhythmia. Hemodialysis was performed daily for 4 days in an effort to remove NAPA. Pacing was continued for 2 days, by which time the procainamide level had decreased to 4.6 mg/liter. Eleven seconds after discontinuation of pacing, VT/VF recurred. After cardioversion, atrial pacing was reinstituted. Eight days after procainamide therapy was discontinued, procainamide was undetectable in serum despite a NAPA level of 15 mg/liter. Pacing was discontinued the next day. VT/VF recurred 90 minutes later (Fig. 1), at a time when procainamide was undetectable and the NAPA level was 12 mg/liter.

Pacing was reinstituted and continued for 5 more days. Procainamide remained undetectable and the NAPA level had decreased to 4.3 mg/liter. No further polymorphic VT or VF was noted after pacing was discontinued. The patient continued to have multiform VPCs and nonsustained VT. Figure 2 is a summary of the relation between drug levels and VT/VF.

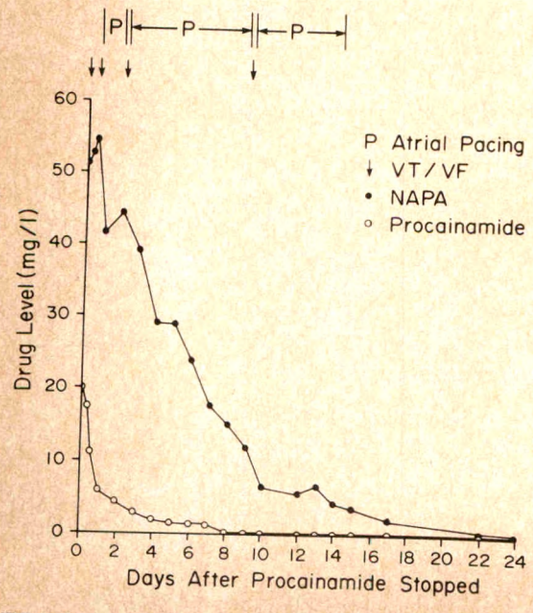

FIGURE 2. Occurrence of ventricular tachycardia/ventricular fibrillation (VT/VF) with decreasing procainamide and N-acetyl procainamide (NAPA) levels and prevention of VT/VF by atrial pacing.

NAPA has antiarrhythmic efficacy independent of its parent drug. The therapeutic range appears to be 10 to 24 mg/liter.[5] Kluger et al[3] reported sudden death in 4 of 19 patients receiving NAPA, but concluded that sudden death represented lack of efficacy rather than worsening of the arrhythmia. Winkle et al[4] reported sudden death in 1 of 11 patients receiving NAPA, but could not prove that NAPA contributed to the death. Olshansky et al[2] reported recurrent polymorphic nonsustained VT without VF in a patient with NAPA levels between 29 and 33 mg/liter, at a time when procainamide levels were as low as 4.1 mg/liter. This report suggested that high NAPA levels could lead to VT but VF was not observed.

In our patient, the first 3 episodes of polymorphic VT and VF could be attributed, at least in part, to procainamide. However, the fourth episode occurred at the time when procainamide had been undetectable in plasma for more than 24 hours. Although polymorphic VT and VF may be seen in a number of disease states, including coronary artery disease,[1] the first appearance of these arrhythmias after the addition of a new drug and the disappearance after adequate washout of the drug is suggestive of a proarrhythmic effect.

The findings in this patient confirm that therapeutic or toxic NAPA levels can cause recurrent VT/VF in sensitive patients, particularly in the setting of chronic renal failure, in which the accumulation of NAPA is well documented.[6] Although hemodialysis is of limited value in the management of NAPA toxicity, overdrive pacing may be lifesaving during the long period required for elimination of NAPA in patients undergoing dialysis.

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Prosthetic Mitral Regurgitation Detected by Doppler Echocardiography

ROBERT P. FERRARA, MD
ARTHUR J. LABOVITZ, MD
ROBERT D. WIENS, MD
HAROLD L. KENNEDY, MD
GEORGE A. WILLIAMS, MD

Doppler echocardiography is a useful means of evaluating cardiac valve function noninvasively.[1,2] The detection of mitral regurgitation (MR) by Doppler techniques has shown high sensitivity and specificity when correlated to the degree of MR determined by contrast ventriculography.[1] However, assessment of prosthetic MR with Doppler echocardiography is more difficult than detection of native valve MR, especially when the tilting disc prosthetic valve has been evaluated, because of difficulty in obtaining Doppler signals from behind the prosthesis.[3] We describe a patient with paravalvular MR around a dehiscent Björk-Shiley mitral prosthesis in which the regurgitant jet was easily detected by Doppler, and the calculated mitral valve orifice increased.

A 64-year-old woman, who had a mitral commissurotomy at age 52 years for mitral stenosis, was doing well until age 62 years (June 1982) when severe dyspnea on exertion developed and she underwent replacement of the stenotic mitral valve with a Björk-Shiley prosthesis. She did well until November 1982, when she had severe congestive heart failure associated with a loud MR murmur. Evaluation revealed S. epidermidis *endocarditis. Abnormal rocking motion of the stent and marked paravalvular leakage was confirmed at cardiac catheterization. A new Björk-Shiley mitral prosthesis was implanted and she received 6 weeks of intravenous vancomycin and rifampin. At the time of discharge, 2-dimensional (2-D) and Doppler echocardiograms documented normal prosthetic valve function, normal flow characteristics across the prosthesis and no MR (Fig. 1, left). She was readmitted 2 weeks later with symptoms of mild congestive heart failure, at which time a soft apical systolic murmur was heard. Two-dimensional echocardiography showed unobstructed valve motion without abnormal stent motion and was unchanged from the previous study. The Doppler examination, however, revealed new regurgitant flow across the prosthetic valve, increased diastolic velocity, and increased mitral valve orifice from 2.0 to 2.2 cm^2 as calculated by the pressure-half time method[2] (Fig. 1, right). Congestive heart failure progressed. Repeat 2-D echocardiography revealed increased systolic motion of the stent (Fig. 2), and the corresponding Doppler study showed regurgitant mitral flow and a further increased mitral valve orifice (2.7 cm^2). Cardiac catheterization confirmed marked paravalvular leakage through the posteromedial aspect of the prosthesis. At surgery the valve was dehisced in its medial aspect. The valve ring was resutured, but the patient died during operation.*

M-mode and 2-D echocardiographic evaluation of mechanical prosthetic valves provides qualitative, but not quantitative, information regarding valve function,[4] and has low sensitivity in detecting paravalvular leak, relying on associated findings such as hyperdynamic left ventricle and septum. Doppler echocardiography correlates well with invasive means in the quantitative evaluation of regurgitant and stenotic native valves.[1–3] Although assessment of regurgitant flow behind a tilting disc prosthesis is difficult, Doppler examination was recently shown to be a sensitive means of detecting prosthetic MR in patients in whom systolic murmurs were heard after valve replacement regardless of the presence or absence of prosthetic MR.[5]

Two interesting features are demonstrated. First, the Doppler evidence for prosthetic MR was present 2

From the Division of Cardiology, St. Louis University School of Medicine, 1325 South Grand Boulevard, St. Louis, Missouri 63104. Manuscript received June 22, 1984; revised manuscript received August 23, 1984, accepted August 27, 1984.

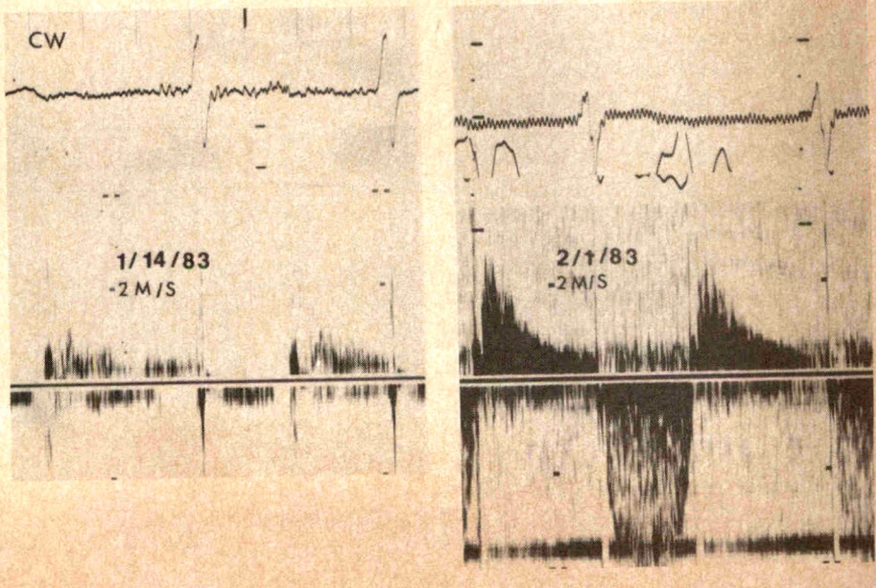

FIGURE 1. Left, apical continuous-wave Doppler tracing of the prosthetic mitral valve before the patient was discharged with a normally functioning prosthesis. Note the low diastolic velocity and absent systolic velocities. **Right,** continuous-wave Doppler tracing of the same valve 2 weeks later. The scale is unchanged. Diastolic velocities have doubled and new systolic velocities are present below the baseline representing new mitral regurgitation. M/S = meters per second.

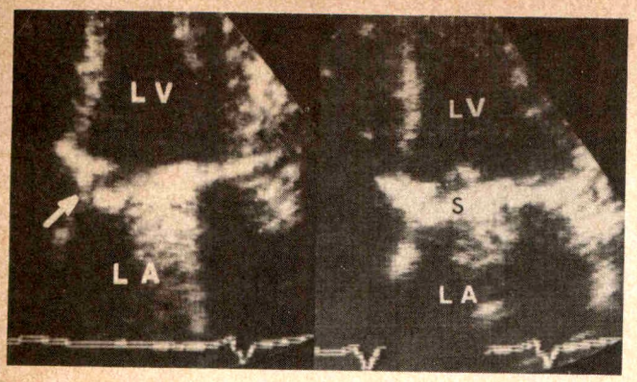

FIGURE 2. Apical view of the mitral prosthesis in systole (**left**) and diastole (**right**) just before the patient's death. Note the clear separation of the valve from the anulus (**arrow**) during systole. LA = left atrium; LV = left ventricle; S = stent.

weeks before the 2-D study revealed abnormal stent motion. Second, in addition to the detection of systolic regurgitant flow, the Doppler study confirmed prosthetic MR by showing a calculated increase in mitral valve area, which is most likely due to diastolic flow around the dehisced stent and through the prosthesis.

Analysis of Doppler flow pattern changes in diastole as well as systole may provide useful information in evaluation of prosthetic mitral valvular dysfunction.

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Tissue Characterization by Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy

DONALD FARMER, MD
CHARLES B. HIGGINS, MD
EDWARD YEE, MD
MARTIN J. LIPTON, MD
DENNIS WAHR, MD
THOMAS PORTS, MD

A method for providing tissue characterization of the myocardium has been sought for years. Magnetic resonance imaging (MRI) has demonstrated excellent soft tissue differentiation and has been proposed as a method for tissue characterization. This capability of MRI is suggested from previous studies that showed changes in signal intensity of ischemic compared with normal myocardium in experimental preparations.[1,2] Measurement of magnetic relaxation times, T1 and T2, in animal studies have verified a difference in these times between normal and ischemically damaged myocardium.[1–3] Recently, we encountered a patient with hypertrophic cardiomyopathy (HC) in whom MRI provided more accurate anatomic depiction of the condition than other imaging techniques. MRI also revealed differences in signal intensity at various sites in the left ventricular (LV) myocardium due to fibrosis and myocardial ischemia.

From the Departments of Radiology, Medicine and Surgery, University of California, San Francisco, California 94143. Manuscript received May 23, 1984; revised manuscript received August 16, 1984, accepted August 23, 1984.

A 62-year-old man was admitted for evaluation of refractory recurrent ventricular tachycardia. Cardiac catheterization at age 48 years yielded findings consistent with HC. A subsequent echocardiogram in 1982 showed an LV aneurysm and a prolapsing mitral valve. During the current admission, 2-dimensional echocardiography showed a dyskinetic apex and an extremely hypertrophied proximal portion and midportion of the left ventricle with systolic cavity obliteration. Cardiac angiography was interpreted as asymmetric encroachment of the cardiac walls upon the LV cavity with division of the chamber into a small-volume, hyperdynamic proximal chamber and a distal akinetic chamber. The 2 major cavities were separated by a wide ring of thickened myocardium in the midportion of the ventricle. The proximal and distal cavities were connected by a narrow

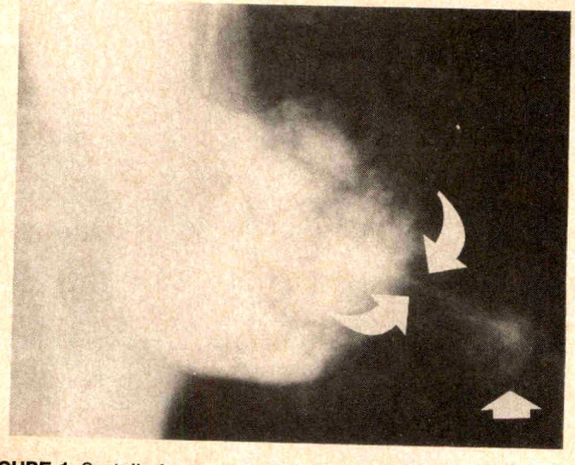

FIGURE 1. Systolic frame of the left ventricular cineangiogram (right anterior oblique projection). There is severe midventricular narrowing producing a small channel (**arrows**), which leads into a small akinetic apical chamber (**arrowhead**).

tunnel coursing through the ring of hypertrophied muscle (Fig. 1). A rare form of HC of the midventricular type was considered, although a cardiac tumor causing the segmentation could not be excluded. The coronary arteriogram revealed no fixed obstruction lesions, but did reveal severe systolic narrowing of an intramyocardial left anterior descending coronary artery.

MRI was performed with a 0.35-tesla superconductive type (Diasonics, Inc.), which gave a resonance frequency for hydrogen of 15 MHz. The multislice imaging technique was used whereby 5 adjacent but not contiguous 7.0-mm-thick tissue sections (2.5-mm gap between slices) were pulsed at 100-ms intervals during each repetition interval (TR). Thus, the imaging period for all 5 sections was approximately 500 ms. This duty cycle of 500 ms was accommodated within the RR interval for this patient. With this technique, the slices are not in the same phase of the cardiac cycle. The sectional (plane) images were reconstructed with the 2-dimensional Fourier transform technique. The reconstruction matrix comprised 128 vertical and 256 horizontal pixels. It was displayed in 256 gray levels, with the brightest area representing the tissue with the greatest MRI signal intensity. Spatial resolution was 1.6 mm. The TR was determined by the RR interval of the electrocardiogram when gated to every heart beat and double the RR interval when gated to every second heart beat. The echo delay times (TE) were 28 and 56 ms.

Magnetic resonance images showed obliteration of the LV cavity by marked thickening of the anterior, anteroseptal and anterolateral walls of the LV myocardium (Fig. 2). At the midventricular level, only the inflow portion was patent, with an anteriorly situated aneurysmal cavity at the apex, connected only by a narrow channel to the residual inflow cavity. This appearance was similar to that shown by left ventriculography (Fig. 1). In addition to defining the anatomic configuration of the ventricle, the images also demonstrated inhomogeneity of the myocardial signal intensity. The upper septum had normal intensity, whereas the anteroseptal region had low intensity. Additionally, there was a region of high signal intensity involving the subendocardial layer of the apical segment (Fig. 2). There was a greater increase in signal intensity of the apical subendocardial layer on the TE 56-ms image than on the TE 28-ms image. This finding is consistent with a long T2 relaxation time of the subendocardial myocardium. High signal intensity and prolonged T2 time were observed in dogs with acute myocardial infarctions[1,2]; these experimental data were the basis of interpretation of the MR study in this case. The observations in the present case and the prior experimental results suggested that the variability of the signal intensity in the myocardium represented fresh ischemic damage in the high-intensity region, while the low intensity region was fibrosis at the site of remote myocardial ischemia injury. In view of the mass effect on the ventricular cavity, the possibility of a myocardial tumor was also considered. The magnetic resonance images (Fig. 3) also provided evidence of stasis of flow in the narrowed LV cavity. Comparison of first (TE = 28 ms) and record (TE = 56 ms) images showed filling of the chamber with high-intensity signal on the second echo image. This finding is consistent with experimental data indicating that this pattern is consistent with flow stasis.[4]

At surgery, a LV apical aneurysm was resected and the apical scar was plicated. Gross examination of the ventricle during bypass revealed areas of tough, fibrous myocardium adjacent to edematous myocardium in the subendocardial layer of the mass of myocardium that nearly obliterated the midportion and distal portion of the left ventricle. Extreme hypertrophy of the myocardium at the base of the papillary muscles was noted. Pathologic examination of the resected portion of the left ventricle revealed marked interstitial fibrosis separating sparse myocardial fibers. The regions found to be edematous by inspection were not biopsied.

A wide spectrum of distribution of HC exists within the left ventricle.[5,6] While asymmetric septal hypertrophy is the most frequent type, several variations of this disease have been uncovered in the past decade, of which the midventricular type is apparently very rare.[5] MRI provided an accurate anatomic assessment in this

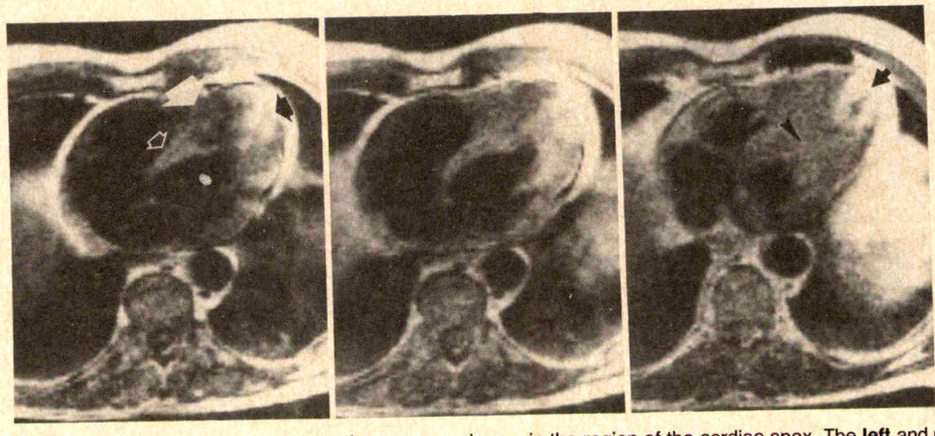

FIGURE 2. Sequential but not contiguous transverse magnetic resonance image in the region of the cardiac apex. The **left** and **middle** panels were produced from the first spin echo (TE = 28 ms); the **right** panel was from the second spin echo (TE = 56 ms). Three areas of signal intensity can be seen within the myocardium (**left**). The upper septum (**open white arrow**) has normal signal intensity, whereas the anteroseptal portion (**white arrow**) shows diminished signal intensity and corresponded to regions of fibrosis at surgery. The region of high signal intensity (**black arrow**) adjacent to the area of anteroseptal fibrosis suggests soft tissue edema secondary to acute myocardial ischemic damage near the apex. In the image on the **right,** which was obtained during ventricular systole, the left ventricular cavity is nearly obliterated in its midportion (**arrowhead**), corresponding to the left ventricular cineangiogram in Figure 1. The small akinetic apical chamber (**arrow**) is rimmed by high signal intensity, suggesting subendocardial edema. There are regions of high signal intensity in the anterior myocardium on all images, suggesting that the area of ischemic damage involves a wide region.

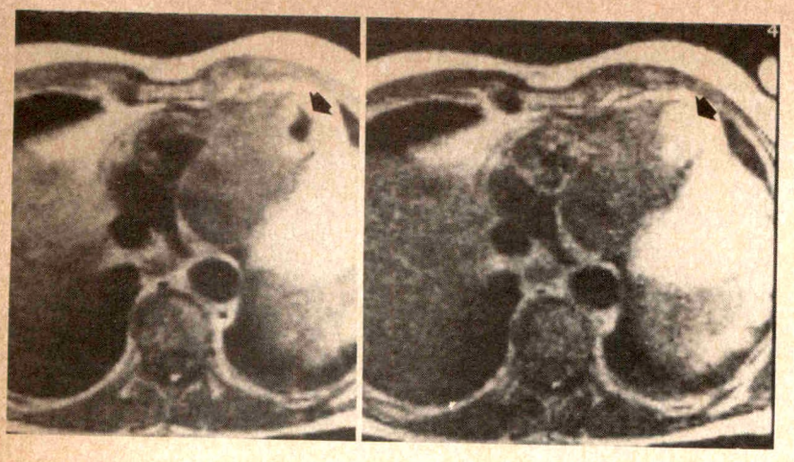

FIGURE 3. Transverse magnetic resonance images at the apical portion of the left ventricle showing obliteration of the inferior portion of the ventricular cavity, leaving only the small akinetic apical chamber. The image produced from the first spin-echo (**left**) (TE = 28 ms) reveals the high-signal intensity rim around the chamber (**arrow**), corresponding to subendocardial edema. In the second spin-echo image (**right**, TE = 56 ms), the chamber is filled with signal secondary to extremely sluggish flow in the akinetic region (**arrowhead**).

unusual case. Previous reports have also indicated that gated MRI provides clear anatomic depiction of cardiac[7] and pericardial abnormalities[8] because it provides high natural contrast between the blood pool and the walls of the heart as a consequence of the virtual absence of magnetic resonance signal from blood flowing at normal velocity.

Perhaps more important in this patient was the variability in myocardial signal intensity, which corresponded to differences in the nature of the tissue in the LV wall. The ability of MRI to discern tissue water content[1,2] and suggest fibrous change in tissues[9] due to alterations in magnetic relaxation times (T1 and T2 times) has been proposed. The current report suggests that this sensitivity to variations in the composition of tissues can provide myocardial tissue characterization in patients.

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Origin of the Right Coronary Artery from the Pulmonary Trunk: Diagnosis by Two-Dimensional Echocardiography

CLIFTON WORSHAM, MD
STEPHEN P. SANDERS, MD
BRUNO M. BURGER, MD

Anomalous origin of the right coronary artery (RCA) from the pulmonary trunk (PT) is rare. Fewer than 20 cases have been reported.[1] Most have been incidental findings at autopsy or during surgery for other reasons.[2–4] Rarely, diagnosis has been made by angiography.[5,6] We report here a patient with the RCA from the PT, diagnosed by 2-dimensional echocardiography (2-D echo).

From the Department of Pediatrics, Harvard Medical School, and the Department of Cardiology, The Children's Hospital, Boston, Massachusetts 02115. Dr. Worsham's present affiliation: Cigna Health Plan, Division of Pediatrics, Phoenix, Arizona. Dr. Burger's present affiliation: Centro Medico Docente La Trinidad, Caracas, Venezuela.

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T.A., a 6.5-year-old asymptomatic girl, was referred because of precordial murmur. Examination disclosed a grade 2/6 blowing midsystolic ejection murmur at the left lower sternal border without radiation. The electrocardiogram showed a QRS axis of +50° without evidence of left ventricular hypertrophy or repolarization abnormalities. The cardiac silouette was minimally enlarged on chest radiograph. A 2-D echocardiogram disclosed a dilated left coronary artery arising from the aorta (Fig. 1A). The right coronary artery, seen in parasternal short-axis view, also was dilated and appeared to course anterior to the aorta to join the PT (Fig. 1B). Doppler examination revealed a diastolic flow disturbance in the PT adjacent to the origin of the RCA. Both ventricles were of normal size and appeared to function normally. Origin of the RCA from the PT was subsequently documented by cineangiography (Fig. 2). A left-to-right shunt (Qp/Qs = 1.4:1) was demonstrated. The end-diastolic pressure was 1 to 4 mm Hg in both ventricles before angiography, but the left ventricular end-diastolic pressure increased to 20 mm Hg after angiography.

Dilatation of the coronary arteries is a distinctive echocardiographic finding that suggests an anomalous

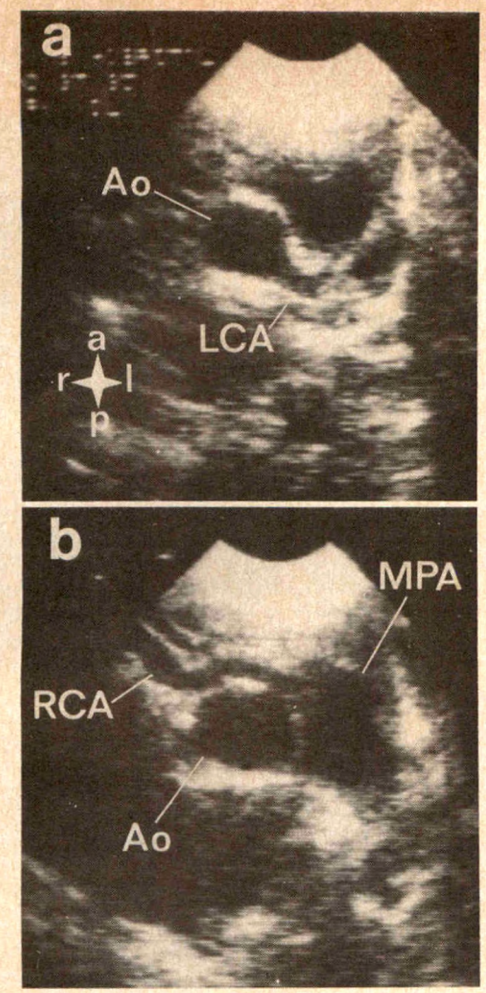

FIGURE 1. a, parasternal short-axis view illustrating the dilated left coronary artery (LCA) connecting with the aorta (Ao). **b,** similar view showing the right coronary artery (RCA) coursing anterior to the aorta to connect with the main pulmonary artery (MPA). a = anterior; l = left; p = posterior; r = right.

origin or fistulous connection of 1 or both coronary arteries.[1] In our patient the left coronary artery was dilated, but it arose from the aorta. The large RCA passed anterior to the aorta to reach the PT. Many planes of examination were used, but no connection between the RCA and the aorta could be demonstrated. Doppler examination confirmed abnormal diastolic flow in the PT.

A prominent conus branch of the RCA may course anterior to the aorta and, due to false dropout, may

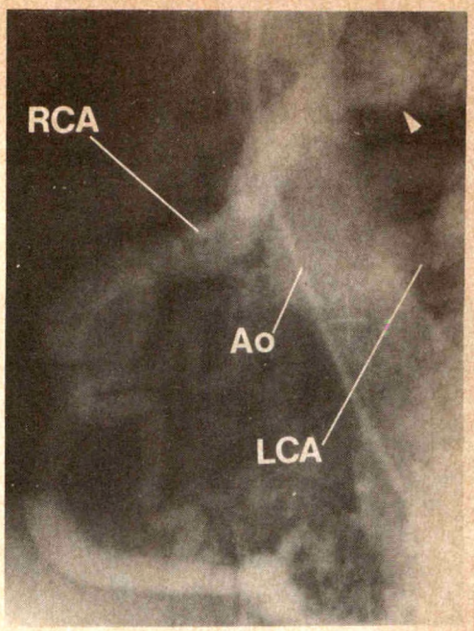

FIGURE 2. Angiogram in left anterior oblique projection showing the anomalous right coronary artery (RCA) passing anterior and to the left of the aorta (Ao) to connect with the main pulmonary artery. A small amount of contrast material can be seen in the main pulmonary artery (**arrow**). LCA = left coronary artery.

appear to connect with the pulmonary artery. Nevertheless, this finding should not be associated with dilatation of the coronary arteries, and careful examination of the right coronary sinus of Valsalva should disclose the origin of the right coronary artery.

The normal left ventricular size at rest and shortening fraction indicates that ventricular size and function are not reliable diagnostic criteria for anomalous origin of a coronary artery.

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Abnormal Position of the Brachiocephalic Vein

JEFFREY F. SMALLHORN, MD
PAOLO ZIELINSKY, MD
ROBERT M. FREEDOM, MD
RICHARD D. ROWE, MD

With the advent of suprasternal echocardiography, both normal and abnormal systemic venous drainage can be delineated noninvasively.[1,2] Persistence of the left superior caval vein (SCV) is readily identified and can be differentiated from a left vertical vein in patients with anomalous pulmonary venous connection.[2,3] Similarly, the absence of a bridging brachiocephalic vein (innominate vein) in the presence of a left SCV is reliably recognized.[1] The left brachiocephalic vein invariably runs in front of the aorta to its point of communication with the right-sided brachiocephalic vein. Rarely, the left brachiocephalic vein has a subaortic course running beneath the aortic arch.[4–6] This study describes cross-sectional echocardiographic features in 7 patients in whom the left brachiocephalic vein ran beneath the aortic arch before communicating with the right brachiocephalic vein.

In the normal patient, in the suprasternal long-axis projection, the left brachiocephalic vein can be seen at its point of communication with the right to form the SCV (Fig. 1a). With anticlockwise rotation the azygous vein can be visualized, just above the SCV right atrial junction (Fig. 1b).

Seven patients were identified in whom the brachiocephalic vein ran beneath the aortic arch. In 6 the aortic arch was right-sided. Abnormalities of the right ventricular outflow tract were the most frequent associated anomalies, although in patient 5, the intracardiac anatomy was normal. In patient 1, the central pulmonary arteries were absent, and the left brachiocephalic vein was the only vascular structure beneath the aortic arch (Fig. 2).

The first clue to the presence of an abnormal position of the brachiocephalic vein was seen in the frontal plane projection, where an absence of the vessel anterior to the aortic arch was noted (Fig. 3a). With closer inspection, the vessel could be seen at its origin on the left, then traced inferiorly and to the right beneath the aortic arch (Fig. 3a). It appeared to communicate with the right brachiocephalic vein at a more inferior site, with the resulting SCV being shorter than

From the Division of Cardiology, Department of Paediatrics, The Hospital for Sick Children, 555 University Avenue, and the Department of Pediatrics, The University of Toronto, Faculty of Medicine, Toronto, Ontario M5G 1X8 Canada. This study was supported by Coordena Gao de Aperfeigoamento de Pessoal de Nivel Superior (Capes), Brazil. Manuscript received May 29, 1984; revised manuscript received September 10, 1984, accepted September 11, 1984.

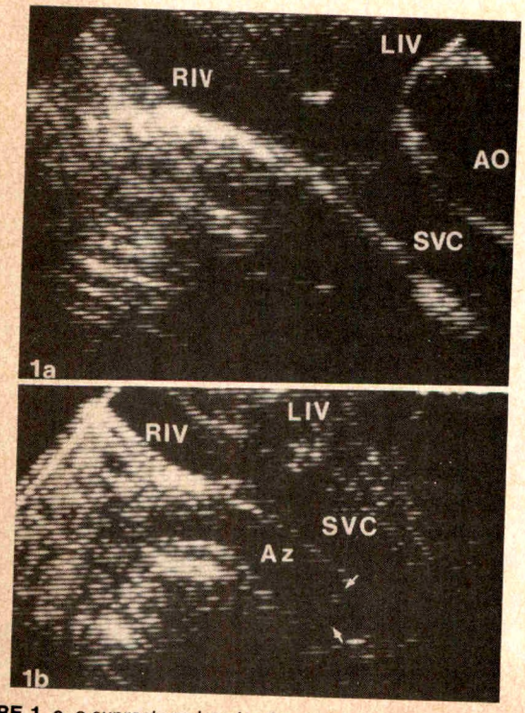

FIGURE 1. a, a suprasternal projection in the patient with a normally positioned left brachiocephalic vein (innominate vein) (LIV). **b,** relation of the azygous (Az) vein to the superior caval vein (SVC). AO = aorta; RIV = right brachiocephalic vein.

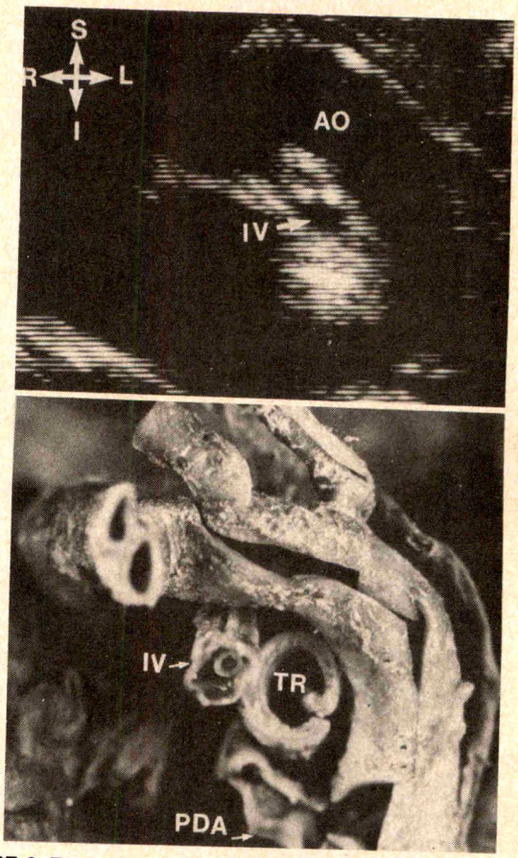

FIGURE 2. Top, suprasternal long-axis projection in patient with an abnormally positioned brachiocephalic vein, pulmonary atresia, ventricular septal defect and absent central pulmonary artery. The only structure seen in the crook of the aortic arch is the left brachiocephalic vein (IV). **Bottom,** anatomic appearance in a different patient. AO = aorta; I = inferior; L = left; PDA = patent ductus arteriosus; R = right; S = superior; TR = trachea.

normal. The azygos vein was situated above the origin of the SCV from the brachiocephalic vein (Fig. 3c), unlike normally, where it lies above the site of entry of the SCV into the right atrium (Fig. 1b). The brachiocephalic vein appeared to run in front of the right pulmonary artery.

In the long-axis projection, in the presence of central pulmonary arteries, the brachiocephalic vein and the pulmonary artery could be seen in their short axis (Fig. 4). In the patient with absent central pulmonary arteries, a solitary vessel was observed (Fig. 2). Confirmation of the abnormality was available in all but patient 5, either at operation or cardiac catheterization. Simultaneous aortic root and brachiocephalic vein angiography demonstrated the abnormality (Fig. 5). Similarly, in 1 patient contrast echocardiography was performed in the left brachiocephalic vein with flow observed beneath the aortic arch (Fig. 3b). The left and right brachiocephalic veins are formed by the confluence of the internal jugular and subclavian veins. The normal left brachiocephalic vein then courses in front of the transverse aortic arch to its site of communication with the right brachiocephalic vein, resulting in the formation of the SCV. The azygos vein arises from the posterolateral aspect of the SCV below the point of communication of the brachiocephalic veins.

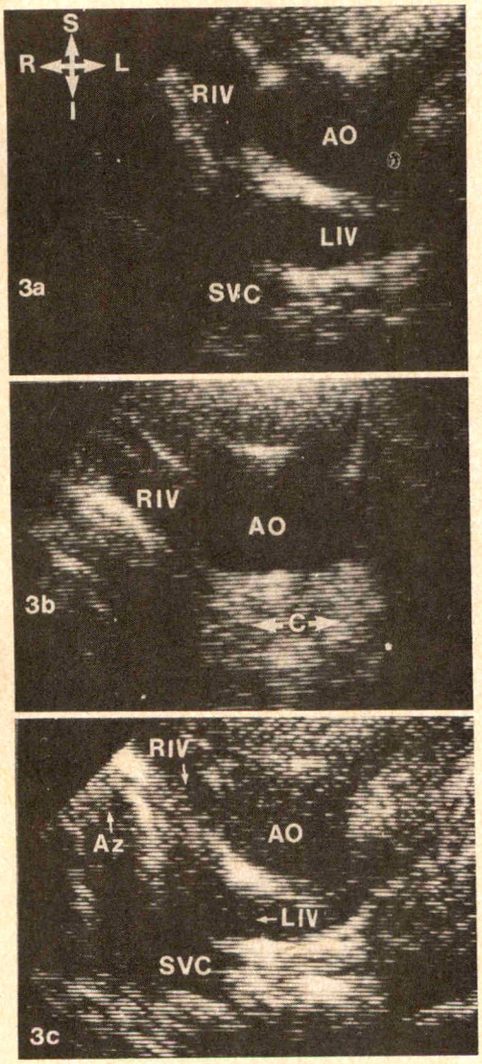

FIGURE 3. a, suprasternal frontal plane projection in a patient with an abnormally positioned left brachiocephalic vein (LIV). Note the absence of a brachiocephalic vein above the ascending aorta (AO). The left brachiocephalic vein runs beneath the aorta before its communication with the right brachiocephalic vein (RIV). Note the resulting short superior caval vein (SVC). **b,** suprasternal frontal plane projection from the same patient after injection of contrast (C) into the left brachiocephalic vein. Note the contrast that opacifies this venous structure, which lies beneath the aortic arch (AO). **c,** a suprasternal frontal plane projection from the same patient demonstrating the azygous (Az) vein which originates from the base of the right brachiocephalic vein (RIV) rather than the superior caval vein (SVC); other abbreviations as in Figures 1 and 2.

Rarely, the left brachiocephalic vein runs inferiorly and to the right beneath the aortic arch, in front of the ligamentum.[4–6] This results in a short SCV with the azygos vein arising from the right brachiocephalic vein, above its site of communication with the left brachiocephalic vein. Approximately 12 cases have been reported.[4–6] Apart from a report of a patient with tetralogy of Fallot with a left aortic arch,[5] the others appear to have been incidental findings in persons with structurally normal hearts.

Previously, 1 case has been described in which suprasternal M-mode echocardiography and contrast studies were performed.[5]

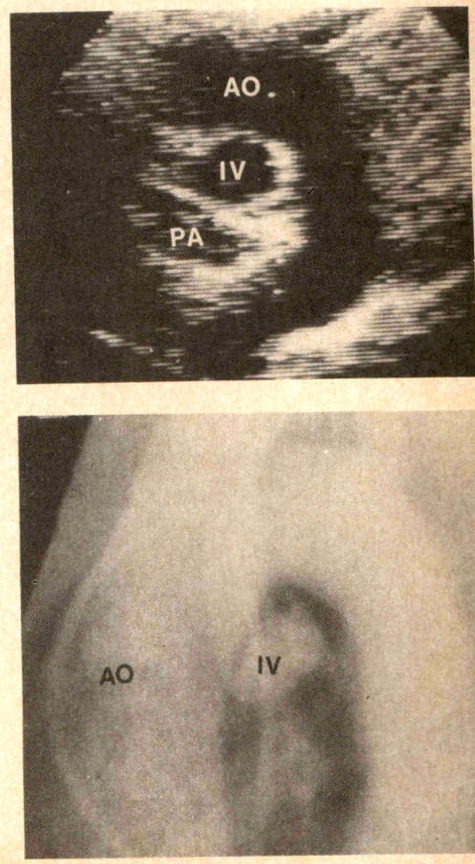

FIGURE 4. Top, a suprasternal long-axis projection in a patient with a left aortic arch, normal sized pulmonary arteries (PA) where the left brachiocephalic vein ran beneath the aortic arch. Note the 2 structures seen beneath the crook of the aortic arch. **Bottom,** angiocardiographic appearance in a different patient. Abbreviations as in Figure 1.

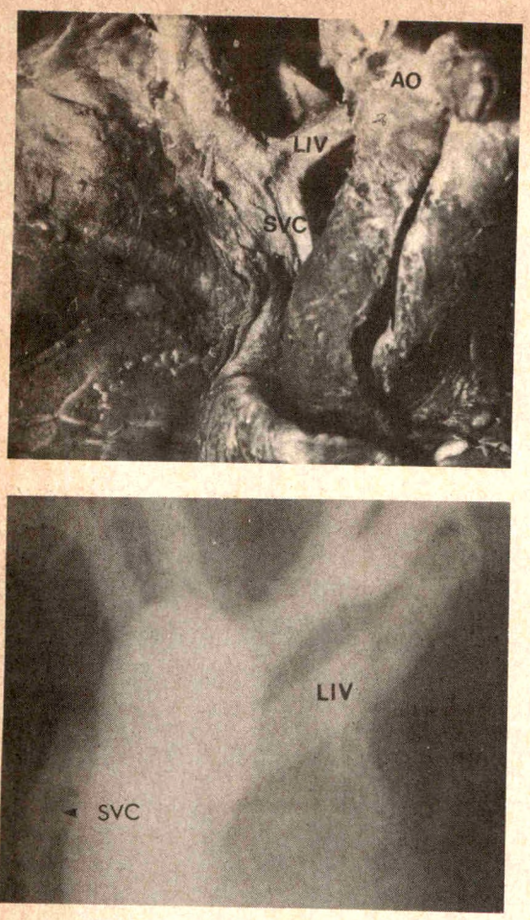

FIGURE 5. Top, anatomic specimen viewed from the front, where the innominate vein runs beneath the aortic arch. This patient also had pulmonary atresia. **Bottom,** simultaneous contrast injection into the aorta and left brachiocephalic vein (LIV).

Systemic venous anomalies are readily identified by cross-sectional echocardiography, particularly the presence of a left SCV and the presence or absence of an associated bridging brachiocephalic vein.[1,2] To our knowledge, this rare anomaly has not previously been described by cross-sectional echocardiography. It is important to differentiate this structure from central pulmonary arteries, particularly in patients with reduced pulmonary flow where they may be absent. If care is not taken, this vessel beneath the aortic arch could be mistaken for a central pulmonary artery, with disastrous results if shunt procedures without prior cardiac catheterization were undertaken.

Abnormal position of the left brachiocephalic vein beneath the aortic arch is a rare anomaly that can be readily identified by suprasternal cross-sectional echocardiography. Care must be taken not to confuse this venous structure with central pulmonary arteries in the presence of pulmonary atresia, or with a venous confluence in total anomalous pulmonary venous drainage, particularly in the presence of right isomerism and reduced pulmonary flow.

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Aortic Dissection in More Than One Family Member

CAROLE A. WARNES, MB, BS, MRCP
PAUL M. KIRKMAN, MD
WILLIAM C. ROBERTS, MD

The occurrence of aortic dissection in 2 or more family members is rare. Such occurred, however, in the father and son described herein.

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and the Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. Manuscript received and accepted September 5, 1984.

Patient 1: *G.J. (father), a 48-year-old white man who was 66 inches tall (168 cm) and weighed 155 pounds (70 kg), died suddenly on November 15, 1983, without previous evidence of cardiovascular dysfunction. At necropsy examination, a horizontal tear, involving about two-thirds of the aortic circumference, was located 2 cm above the sinotubular junction (Fig. 1), and a medial acute aortic dissection extended from this tear to just proximal to the origin of the innominate artery. The outer media and adventitia in the area of the tear ruptured and 300 ml of blood was present in the pericardial sac. A second dissection (clinically silent), which had healed, involved the descending thoracic and abdominal portions of the aorta. The entrance into the false channel was a tear located just distal to the origin of the left subclavian artery. The heart weighed 440 g and the aortic valve was 3-cuspid and normal. Histologic study of the ascending aorta disclosed it to be normal (Fig. 2).*

Patient 2: *T.J. (son), a 22-year-old student, died on March 25, 1983, after the sudden onset of severe chest pain. He was*

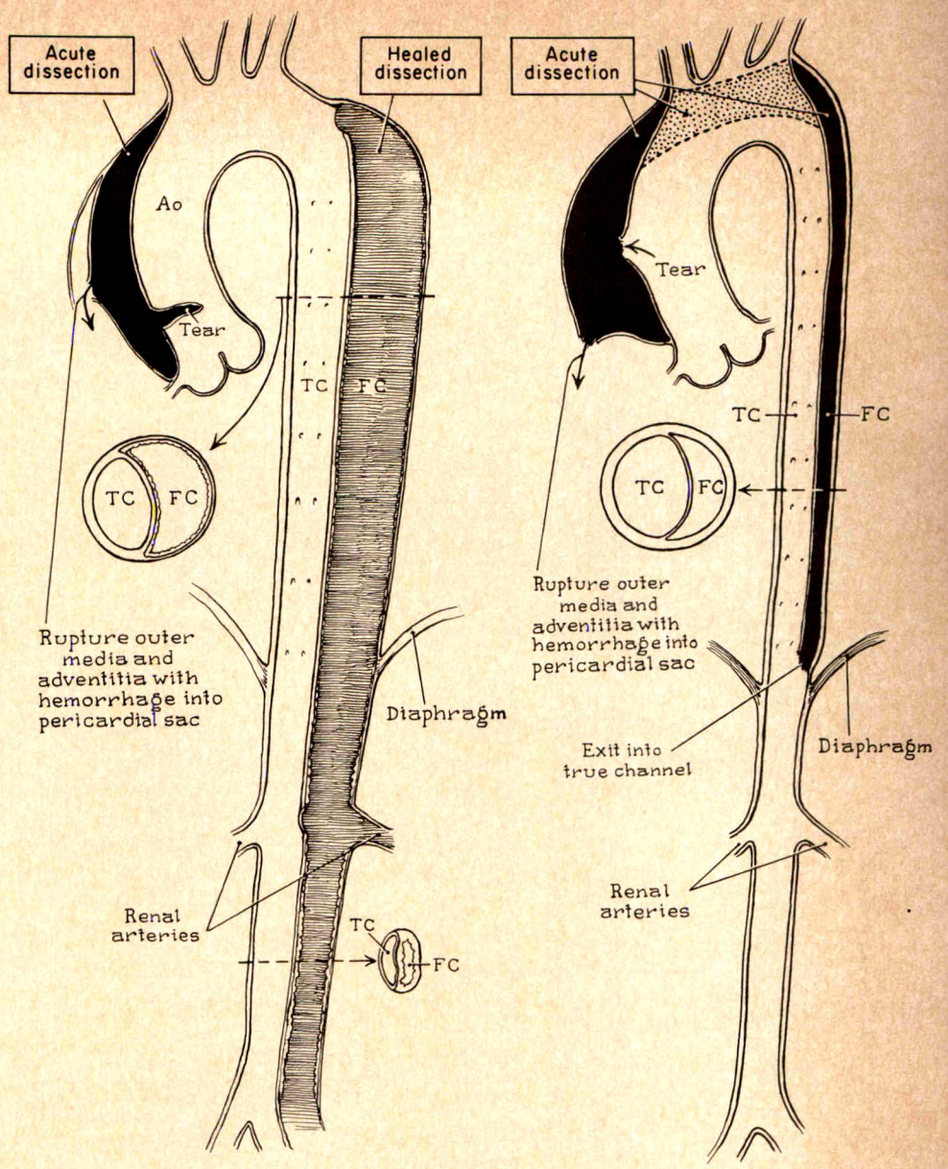

FIGURE 1. Left, drawing illustrating 2 dissections in the father. An acute dissection, which ruptured, began with a tear 2 cm above the sinotubular junction. The healed dissection began in the descending thoracic aorta and involved the entire aorta thereafter. **Right,** drawing illustrating the acute dissection in the son, which began 4 cm above the sinotubular junction and extended to the diaphragm. Ao = aorta; FC = false channel; TC = true channel.

70 inches (178 cm) tall and weighed 175 pounds (80 kg). He had an acute aortic dissection beginning with a tear about 4 cm above the sinotubular junction and extending almost to the level of the celiac axis (Fig. 1). The heart weighed 400 g and the aortic valve was 3-cuspid and normal. Histologic study of the ascending aorta disclosed medial change typical of "cystic necrosis" (Fig. 2).

Neither of these 2 patients or other family members had skeletal or ocular features of the Marfan syndrome (Fig. 3). A search for previous publications describing aortic dissection in more than 1 family member disclosed 12 such reports.[1–12] In the 12 families, 9 of the 26 family members had features highly suggestive of, or diagnostic of, the Marfan syndrome[5,6,8–10]; the 3 patients in the same family reported by Bixler and Antley[12] clearly did not have features of the Marfan syndrome; insufficient information was provided in the remaining 14 patients to be certain about the presence or absence of the Marfan syndrome.[1–4,7,11] Of the 26 patients, at least 24 had died and necropsy was performed in 23.[1–12] The age at death in the 9 parents (6 mothers, 3 fathers)[2,3,5,7–12] and the 1 parents' sister[7] ranged from 31 to 67 years (mean 49), and the ages in the 14 deceased children ranged from 13 to 45 years (mean 29).[2,3,5,7–12] Of the 26 family members, 11 (42%) were women[3,6–10,12] (the age range of the 9 who died was 30 to 62 years [mean 44]) and 15 were deceased males (aged 13 to 67 years [mean 33]).[1–9,11] Of the 24 patients in whom the information was available, the tear was located in the ascending aorta in 18 (69%)[1,2,5–12] and in 13 of them it appears that the entire aorta was involved by the dissection[2,3,5–12]; in the other 6 patients, the tear was in the descending thoracic aorta.[3,4,9,12] More than 1 aortic dissection appeared to have occurred in 3 of the 26 pa-

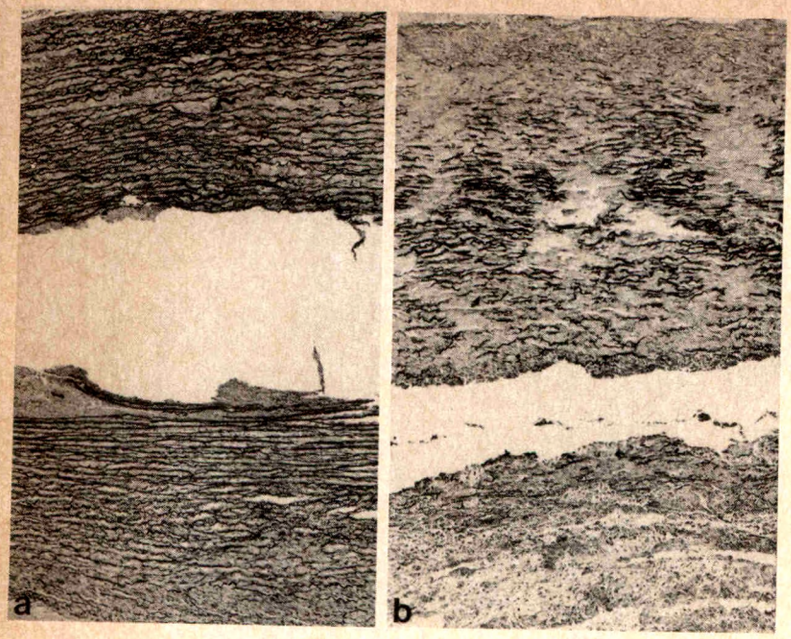

FIGURE 2. Transverse sections of ascending aorta of the father (**a**) and the son (**b**). The configuration of medial elastic fibrils (black) in the father are normal and they are interrupted by fibrous tissue in the son. The space represents the site of dissection. Elastic van Gieson stain; original magnification ×54, reduced 25%.

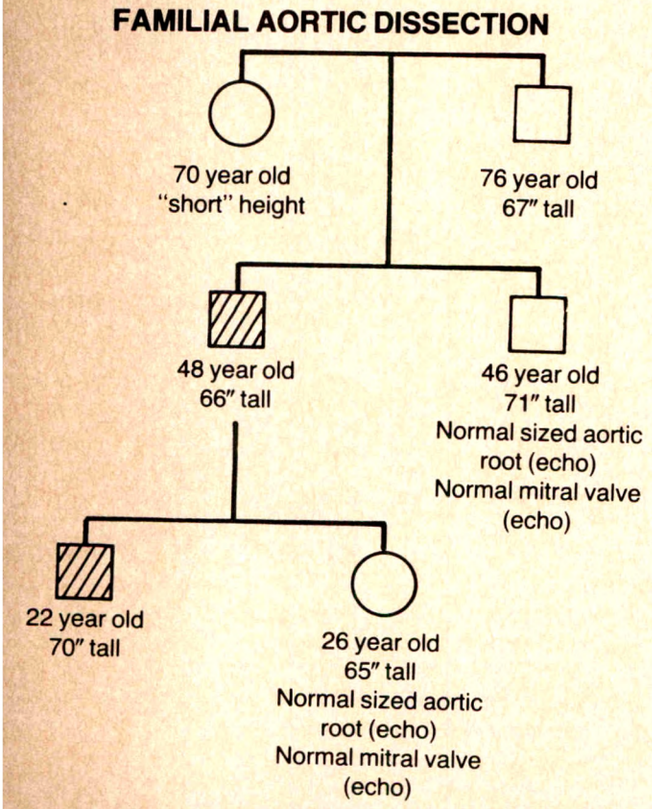

FIGURE 3. Family pedigree. **Squares** and **open circles** are males and females, respectively. **Cross-hatching** denotes the father and son described herein.

tients.[6,8,9] Histologic examination of aorta (portion not always specified) was performed in 20 patients; "cystic medial necrosis" was stated to be present in all 20 (100%). In 1 of our 2 patients, the aortic media was normal histologically. Our 2 patients are particularly unusual in that no family member had features of the Marfan syndrome.

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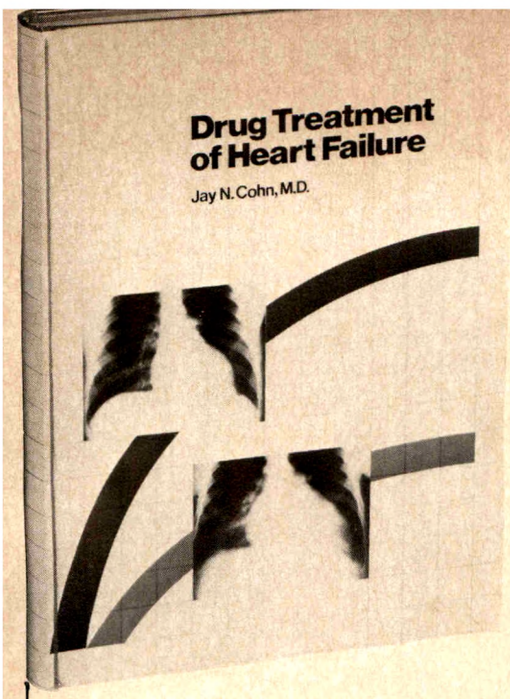

Drug Treatment of Heart Failure

edited by Jay N. Cohn, MD

0-914316-41-9, approx. 250pp., Oct. '83, $35.00

This volume is aimed at providing clinicians with the physiologic and pharmacologic background necessary to effectively and efficiently create and administer drug therapy regimens for their patients who suffer heart failure. All efforts were made to ensure that the timeliness of each chapter, prepared by internationally respected clinicians and medical scientists, would not be compromised by delays in publication. Consequently, this book presents the very latest thinking on the utilization of drug therapy for heart failure and contains many references as recent as 1982 and 1983. This book is highly recommended to all physicians presently treating patients with heart failure.

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Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE
Visken® (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/ kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

	Total (Volunteered and Elicited)		
Body System/ Adverse Reaction	**Visken (pindolol) (N = 322) %**	**Active controls* (N = 188) %**	**Placebo (N = 78) %**
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

* Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

More than 7 million patient-years of experience

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and non-thrombocytopenic purpura.

Gastrointenstinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a beta$_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥ 80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 5 mg b.i.d. alone or in combination with other antihypertensive agents. An antihypertensive response usually occurs within the first week of treatment. Maximal response, however, may take as long as or occasionally longer than two weeks. If a satisfactory reduction in blood pressure does not occur within 3-4 weeks, the dose may be adjusted in increments of 10 mg per day at these intervals up to a maximum of 60 mg per day.

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As a result, PROCARDIA can significantly reduce your patient's angina attack rate and need for nitroglycerin!

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Primary Protection in
MIXED ANGINA

Please see PROCARDIA® (nifedipine) brief summary on next page.

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Usual Effective Dosage: 30 to 60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases.

A Favorable Safety Profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

Reference:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 106:644-652, 1983.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA (nifedipine). This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has been demonstrated.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered. However, the relationship to PROCARDIA therapy is uncertain.

When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and placental abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, allergic hepatitis, and gingival hyperplasia. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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Reversible Right Ventricular Outflow Tract Compression by Immunoblastic Sarcoma

PATRICIA C. COME, MD
STEVEN E. COME, MD
MARILYN F. RILEY, BS
LISA V. CARL, BA
SHOICHIRO NAKAO, MD

Various types of tumors, including lymphomas, carcinomas, sarcomas, thymic cysts, thymomas and fibrolipomas, have been detected by echocardiography within the pericardial space or adjacent to the parietal pericardium.[1–6] Echocardiographic recognition of compression of cardiac chambers by extracardiac tumor has been reported in several patients.[1–4] In the patient reported herein, who had an immunoblastic sarcoma, abnormalities indicative of right ventricular (RV) outflow tract obstruction on physical examination, imaging echocardiography and Doppler echocardiography disappeared in association with complete remission of tumor during chemotherapy.

From the Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of the Beth Israel Hospital, Department of Medicine, Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts.
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A 34-year-old man was admitted with a several-month history of dry cough, exertional dyspnea and fatigue, pruritus, sweating and a 10-pound weight loss. His heart rate was regular at 104 beats/min, and blood pressure was 120/75 mm Hg, without pulsus paradoxus. There was no jugular venous distention. On cardiac examination, a palpable impulse was felt along the right sternal border only. Heart tones were audible over the right chest, where a fourth heart sound and a grade 4/6 long and mid-peaking systolic ejection-quality murmur were also maximal in intensity. There was no significant adenopathy. Electrocardiographic findings were unremarkable. Chest x-ray revealed a large superior mediastinal mass that displaced the heart to the right. Echocardiographic study revealed posterior displacement of the heart by an 8-cm-diameter mass. RV compression was evident on long- and short-axis parasternal views (Fig. 1). Doppler flow study detected marked turbulence distal to the narrowing (Fig. 2). Biopsy revealed immunoblastic sarcoma of T cell type.

With combination chemotherapy, the symptoms, mass and murmur disappeared. Repeated echocardiographic study revealed disappearance of both the mass and the RV compression (Fig. 1). Doppler study revealed a normal flow signal in the RV outflow tract (Fig. 2).

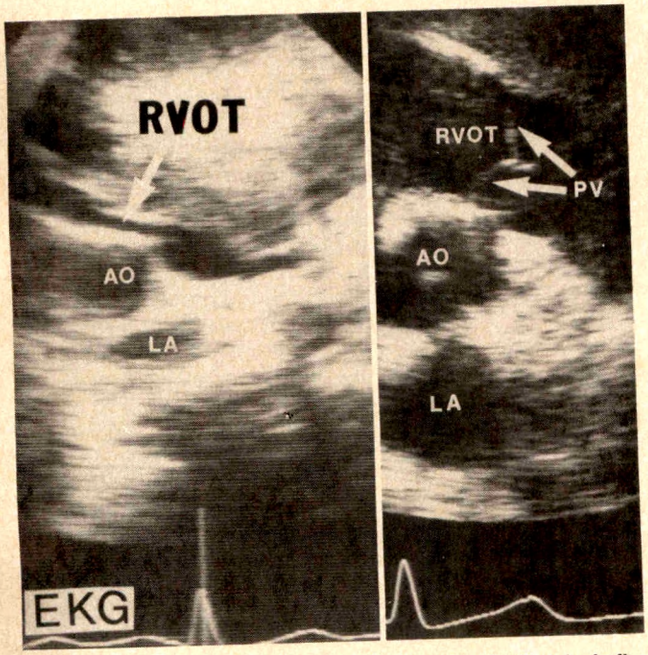

FIGURE 1. Short-axis views at the base of the heart in diastole. **Left,** before chemotherapy, an 8-cm-diameter mass is seen to lie anterior to and to compress the right ventricular outflow tract (RVOT). The pulmonic valve (PV) could not be identified in this plane. **Right,** after chemotherapy, the anterior mass has disappeared and the RVOT has returned to normal size and shape. AO = aortic root; EKG = electrocardiogram; LA = left atrium.

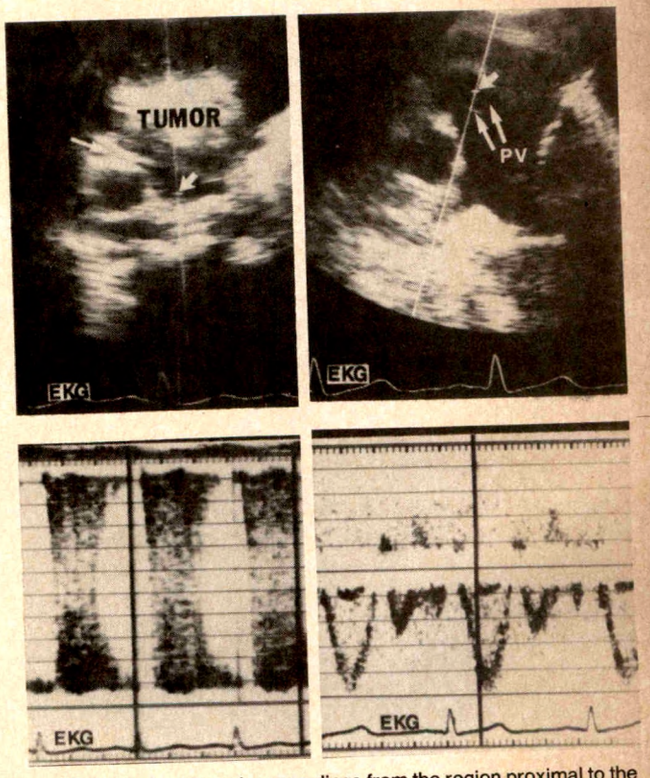

FIGURE 2. Pulsed Doppler recordings from the region proximal to the pulmonary valve leaflets. The **top** tracings, recorded before (**left**) and after (**right**) chemotherapy, illustrate the position of the sample volume (**unlabeled white arrow**). The **bottom** tracings demonstrate the recorded Doppler signals. The 0 reference line is centrally placed in the **right** panel, but has been shifted in the **left** diagram. Each of the **vertical lines** represents 0.5 kHz. The Doppler recording before chemotherapy reveals marked systolic spectral broadening, while that after regression of tumor demonstrates laminar systolic flow. Despite a likely less favorable angle to flow, the kHz shift is greater before chemotherapy than after tumor regression, compatible with tumor-induced obstruction to right ventricular ejection. EKG = electrocardiogram; PV = pulmonic valve.

In our patient, manifestations of subpulmonic stenosis were produced by extrinsic compression of the RV outflow tract by sarcoma. The ejection murmur was long and mid-peaking, compatible with obstruction. On the echocardiogram, the RV outflow tract appeared slit-like in both long- and short-axis views, with its superior border convex toward the lumen. During chemotherapy, RV outflow tract size and shape normalized in association with tumor disappearance. Initial Doppler echocardiography showed marked turbulence proximal to the pulmonary valve. Peak flow velocity could not be determined because cardiac displacement by the tumor made it impossible to orient the Doppler beam in-line with flow. After tumor disappearance, the Doppler beam could be aligned with the presumed direction of flow. The resultant flow signal demonstrated laminar flow, with a lower maximal kHz shift than before chemotherapy, again compatible with disappearance of obstruction.

Imaging echocardiography has greatly facilitated recognition of cardiac involvement by tumor. Doppler echocardiography promises to provide additional information regarding chamber or valvular obstruction or valvular regurgitation in this setting.

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Some Unanswered Problems with Probability Analysis: Possible Impact on Exercise Thallium Test Use

RICHARD M. STEINGART, MD
SHUNICHI HOMMA, MD

Probability analysis has been advanced as a means of selecting patient-test combinations that most efficiently lead to a diagnosis in patients with suspected coronary artery disease (CAD).[1] Results of exercise cardiovascular nuclear medicine tests have yielded the greatest shifts in disease likelihood among patients with intermediate pretest likelihoods for disease. Furthermore, the differences in posttest probability produced by nuclear and electrocardiographic exercise tests are greatest among patients with intermediate pretest likelihoods for disease. However, when we examined the actual use of exercise thallium scintigraphy, most patients referred by both house staff and attending physicians had either very high or low pretest likelihoods for disease.[2] One explanation for these ordering practices is a lack of familiarity with probability analysis.[3] Alternatively, the clinical efficacy of a test may not be valued in proportion to its ability to alter disease likelihood. For example, exercise thallium scintigraphy has been advocated as a valuable means of excluding significant coronary disease, particularly when the pretest likelihood for coronary disease is relatively low.[4] In this study we asked house staff to calculate the predictive value of an exercise thallium test result. We then examined the relation between likelihood estimates and stated preferences for testing in an attempt to discover motivations for test ordering in actual practice.

Twenty-six residents in internal medicine, consecutively encountered on the medical service, agreed to fill out a questionnaire in the presence of 1 of the investigators. Subjects were given 4 brief patient histories (Table I) and published values (± standard deviation) for pretest disease likelihood.[5] They also were given the definitions of test sensitivity and specificity in the laboratory at this institution (sensitivity 0.76, specificity 0.88).[2] The subjects were asked to calculate the predictive value of test results for CAD presence, given that patients 1 to 3 had positive test results and patient 4 had a negative test result. The subjects were informed that they should only consider the results as positive or negative because no further information could be gleaned from the test. They were then asked in which patient the thallium exercise test was most useful. Subjects' estimates of predictive values were gathered using a rating scale from 0 to 100%, in divisions of 10%. For each patient, a range of possible posttest likelihoods was calculated by the investigators. This range was determined by using the upper and lower limits of the confidence intervals for pretest disease likelihood in Bayes' theorem (Table II). Any housestaff answer that was within this range was considered correct (Fig. 1).

Study results are presented in Figure 1. Subject performance was best when the thallium test results confirmed an already high (case 3) or low (case 4) pretest likelihood for disease. Greater difficulty was encountered when the test result conflicted with the clinical diagnosis (case 1), or the patient had an intermediate pretest likelihood for disease

From the Division of Cardiology and Department of Nuclear Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210th Street, Bronx, New York 10467.

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TABLE I Data Provided to House Staff

Pt	Age (yr) & Sex	Hypothetical Patient Problems: Substernal Chest Pain?	Clearly Related to Exertion?	Relieved by TNG?	Disease Prevalence (mean ± SD)[5]	Thallium Test Result
1	35F	+	0	+	4 ± 1	+
2	55M	+	0	+	59 ± 2	+
3	55M	+	+	+	92 ± 1	+
4	45F	+	+	0	13 ± 3	0

TNG = nitroglycerin; + = positive; 0 = negative.

TABLE II Bayes' Theorem

$$\text{Probability of disease given a positive test} = \frac{\text{Sensitivity} \times \text{prevalence}}{(\text{Sensitivity} \times \text{prevalence}) + (1\text{-specificity}) \times (1\text{-prevalence})}$$

$$\text{Probability of disease given a negative test} = \frac{(1\text{-Sensitivity}) \times \text{prevalence}}{((1\text{-Sensitivity} \times \text{prevalence}) + (\text{specificity} \times (1\text{-prevalence}))}$$

(case 2), indicating that the extent to which test results would influence disease likelihood was not precisely understood.

House staff were then asked in which of the 4 patients was the test most useful. Although case 2 was the 1 most frequently selected (12 of 26), most house officers chose a patient at the extremes of pretest disease likelihood (4 each chose cases 1 and 3; 5 chose case 4). One house officer believed the tests to be equally useful. The 4 subjects who selected case 1 (actual posttest likelihood 22%) as most useful overestimated this patient's posttest likelihood at 70%, compared with estimates averaging 21% for those subjects not choosing this testing situation. The 9 subjects who chose cases 3 or 4 as most useful estimated that the test result would slightly increment the diagnostic certainty. The 12 subjects who chose case 2 as most useful estimated the posttest likelihood at 77%, as did those subjects who believed such a test was not particularly useful.

This study demonstrates that house staff estimates of predictive value are accurate only when test results reinforce an already strong clinical impression. The calculations for case 2, the best testing candidate, usually underestimated the power of the test, while those for case 1 often overestimated its power. This overestimation was associated with the preference for testing. However, philosophical differences, rather than differing mathematical abilities, appeared to dictate the preferences of most of the house officers. Despite underestimating the predictive value of the test result in case 2, nearly half valued the marginal value of the positive result in a patient with a truly intermediate chance of having disease. For the remainder, this increment in disease likelihood was not sufficient, and the results in cases 3 and 4 that changed the likelihoods only slightly, but left the least diagnostic uncertainty, were most valued.

Thus, despite extensive attention in the literature, physicians in training are frequently imprecise in the calculation of the predictive value of a test result. At times, these errors appear to contribute to improper test utilization. Many subjects did value the use of the test in the circumstance where, in probabilistic terms, it had the most to offer. However, one-third opted for greater diagnostic certainty, i.e., a more extreme posttest likelihood. These results have implications regarding the threshold approach to clinical decision making. Some studies have examined the use of exercise tests in moving patients above or below somewhat arbitrarily defined threshold probabilities for CAD of 0.90 or 0.10, respectively.[6] Our clinical experience,[2] and the results of the present study, show that physicians often begin testing beyond these thresholds. Because the number of patients with extreme pretest likelihoods is potentially vast, the efficacy of nuclear exercise tests for the diagnosis of CAD should be critically reexamined in this population.

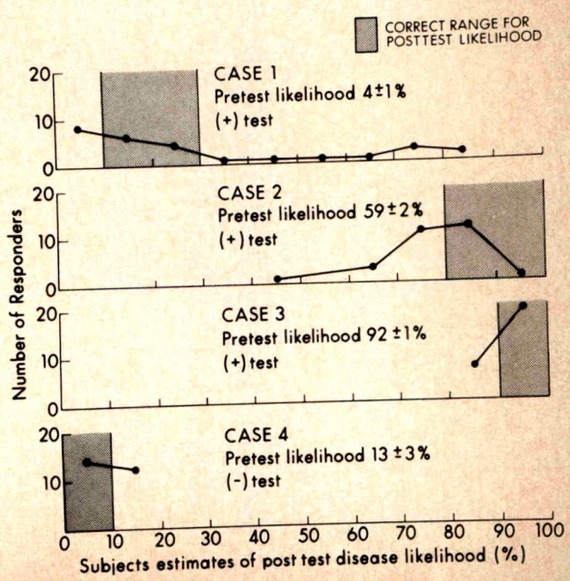

FIGURE 1. House staff estimates of posttest disease likelihood given the published figures for pretest likelihood and test accuracy.

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Detection of Atrial Myxoma by Magnetic Resonance Imaging

PETER W. PFLUGFELDER, MD, FRCP(C)
GERALD WISENBERG, MD, FRCP(C)
DEREK R. BOUGHNER, MD, PhD, FRCP(C)

Magnetic resonance (MR) imaging is beginning to show promise for cardiac imaging[1,2] and may offer a high-resolution alternative for the detection and classification of intracardiac masses.

A 45-year-old woman was admitted to the hospital for investigation of chest pain. Examination and electrocardiogram at rest were normal. A submaximal exercise stress test (Bruce protocol), terminated because of fatigue, yielded borderline positive results. A 2-dimensional echocardiogram demonstrated a 2- to 3-cm sessile left atrial (LA) mass adherent to the atrial septum. Cardiac catheterization and coronary arteriography revealed normal coronary arteries. Cardiac fluoroscopy raised the suspicion of calcific deposits in the region of the mass. Forward pulmonary angiography failed to demonstrate an abnormality.

Cardiac MR images were acquired using a Technicare prototype 0.15T (6.25 MHz) resistive MR instrument. Imaging pulse sequences were initiated by an electrocardiographic signal using a modified Honeywell TT-31 telemetry transmitter and receiver. Images were obtained as 2-dimensional single slices using the spin echo (TE 30 and 60 ms) technique in the transverse, sagittal and coronal planes. Imaging was done at end-systole to capture peak atrial filling. Each image required 6 to 8 minutes for acquisition using 4 signal averages per data point. Total study time was 90 minutes. Cardiac and mediastinal anatomy was well defined (Fig. 1). A large, sessile, high-intensity LA mass was clearly seen along the atrial septum. In the TE 60-ms image, normal myocardium is not well visualized, but the mass is highlighted. In this image, a peripheral area of reduced signal is seen in the tumor.

At surgery, a broad-based LA myxoma was found and re-

From the Department of Medicine, Division of Cardiology, St. Joseph's and University Hospitals, University of Western Ontario, London, Ontario, Canada. Manuscript received May 18, 1984; revised manuscript received August 29, 1984, accepted August 31, 1984.

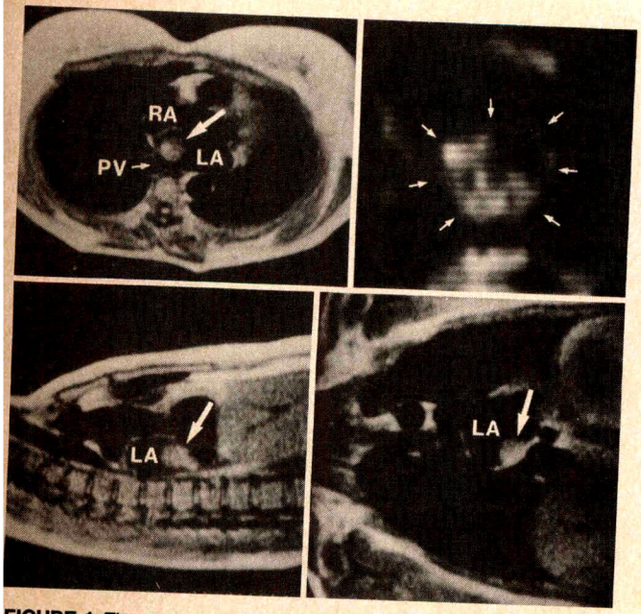

FIGURE 1. The appearance on magnetic resonance imaging of a large left atrial myxoma (**small arrow**) in the transverse (**top left**), sagittal (**bottom left**) and coronal (**bottom right**) planes. These images were obtained using the TE 30-ms sequence. In the TE 60-ms sequence, the tumor is highlighted (**top right**), while normal myocardium is not. LA = left atrium; PV = pulmonary vein; RA = right atrium.

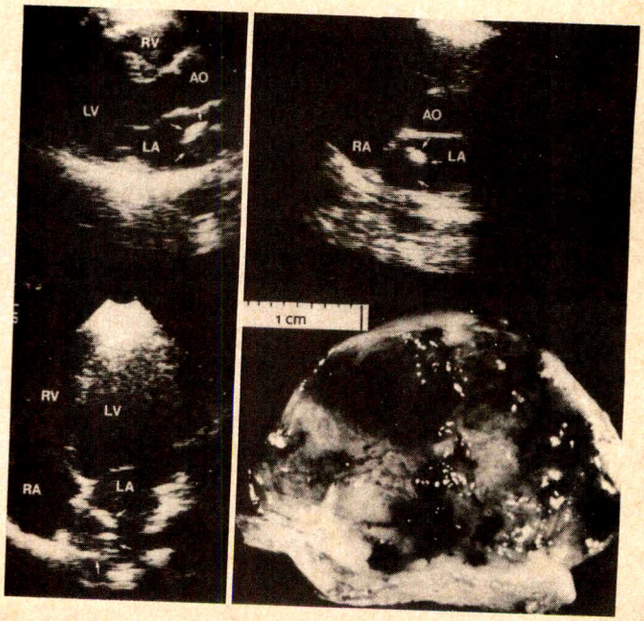

FIGURE 2. Echocardiographic appearance of the myxoma in the parasternal long-axis (**top left**), short-axis (**top right**) and 4-chamber (**bottom left**) views. **Bottom right,** the tumor sectioned in mid-body. AO = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

sected along with a portion of the atrial septum and LA free wall. Anatomic localization, particularly the relation to the pulmonary vein, was accurately predicted by the MR study. The 3-cm neoplasm contained calcific deposits and areas of hemorrhage (Fig. 2). Microscopic examination revealed the typical appearance of myxoma.

Detection of a LA myxoma by MR imaging has not previously been reported. As the present case illustrates, this technique provides a high-resolution means of detecting intracardiac masses.

MR image signal intensity depends on tissue proton density as well as proton characteristics, termed magnetic relaxation times—T1 and T2. Relaxation times of neoplastic tissue are generally altered, allowing distinction from normal tissue, although specificity for pathologic diagnosis is lacking.[3,4] Characterization and classification of intracardiac masses on the basis of MR relaxation variables has yet to be undertaken. Further experience in this regard will define the potential of MR imaging for providing diagnostic information beyond that of current cardiac imaging techniques.

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The AJC in January 1960

WILLIAM C. ROBERTS, MD, and PAUL A. TIBBITS, MD

The January 1960 issue of the AJC contained 19 articles, 11 of which concerned coronary heart disease. The lead article, by Charles Bailey and associates,[1] from Philadelphia, was entitled "Thromboendarterectomy for Coronary Artery Disease." Three years earlier Bailey and associates[2] had reported the first patient to survive coronary endarterectomy and in the present article the results of *coronary endarterectomy* in 15 patients were decribed: 13 patients survived the operation, 1 patient died 8 months postoperatively and 11 were "improved" by the procedure. Of the 15 patients, endarterectomy was performed in 1 coronary artery in 8 patients (left anterior descending in 5) and in 2 or more arteries in 7 patients. A photograph (their Figure 10) showed the endarterectomy specimens in 1 patient to be impressive. The right coronary endarterectomy specimen was 5 cm long and the combined left main and left anterior descending specimen was 9 cm long. The accompanying photomicrograph showed that a portion of media as well as intimal plaque was included in the "endarterectomy" specimen. The procedure was done under complete circulatory bypass. The preoperative angiograms were aortic root injections, not selective coronary arterial injections of contrast material. These extensive coronary endarterectomy procedures combined with aortocoronary bypass are now being performed by Dudley Johnson in Milwaukee, but combined with bypass.

Sigler,[3] from Brooklyn, described 8 necropsy patients with *rupture of the left ventricular free wall during acute myocardial infarction* (AMI). He emphasized the presence of systemic hypertension as the common underlying factor in his patients and in previously reported ones. Now, 25 years later, little additional information has appeared concerning why cardiac rupture occurs in some patients during AMI and not in others. We suspect that the frequency of cardiac rupture during AMI is increasing because arrhythmias, at least during the period of AMI, are far better controlled since the introduction of coronary care units in 1966.

Imperial and associates,[4] from Cleveland, described the frequency of and type of *rate, rhythm and conduction disturbances* as determined by 1 or more random 12-lead electrocardiograms recorded during the first 72 hours of AMI in 153 patients. Some form of disturbance in rate, rhythm or conduction developed in 112 of the 153 patients (73%) and certain forms of disturbances correlated well with the location of the AMI, i.e., whether it involved the anterior or posterior left ventricular wall. Of the 41 patients who had no rhythm or conduction disturbance, 2 (5%) died within 2 years of the AMI; of the 112 patients with a rhythm or conduction disturbance or both, 51 (46%) died within 2 years of the AMI. The frequency of the rate, rhythm and conduction disturbances in the 153 patients was: sinus tachycardia, 28%; sinus bradycardia, 15%; ventricular premature complexes, 12%; atrial fibrillation or flutter, 10%; supraventricular tachycardia, 1%; nodal rhythm, 1%; ventricular tachycardia or fibrillation, less than 1% (1 patient); right bundle branch block, 8%; left bundle branch block, 0, and atrioventricular block, 7% (5 of 10 patients, complete). Continuous electrocardiographic monitoring with the advent of coronary care units, of course, has disclosed the frequency of certain arrhythmias to be much higher than described 25 years ago—ventricular premature complexes by continuous monitoring during AMI has occurred in more than 75% of the patients and ventricular tachycardia in about 25%, for example. Nevertheless, this detailed study by Imperial and associates is important.

Scherf and Bornemann,[5] from New York City, described electrocardiographic results of *blows to the chest after cardiac standstill.* Their 11 case studies and canine experiments clearly demonstrated that mechanical stimulation of the heart offers an immediate, simple, and effective method of cardiac resuscitation during standstill.

An interesting geographic necropsy study by Thomas and associates[6] *compared the frequency of coronary atherosclerosis and myocardial infarcts to the frequency of venous thrombosis and pulmonary embolism* in 3 population groups. The incidence of both acute and healed myocardial infarcts was high in white patients from St. Louis, intermediate in black patients from St. Louis and virtually nil in black patients from Kampala, Uganda, studied at necropsy. The incidence of venous thrombi and pulmonary emboli closely paralleled the incidence of myocardial infarcts in the 3 groups, suggesting that differences in the general tendency of the blood to clot and/or lyse account, at least in part, for the differences in incidences of intravascular thrombosis in the autopsied patients from Uganda and St. Louis.

Stephenson and associates,[7] from Nashville, subjected 330 dogs to 30 minutes of occlusion of their left anterior descending coronary artery. Of 239 dogs

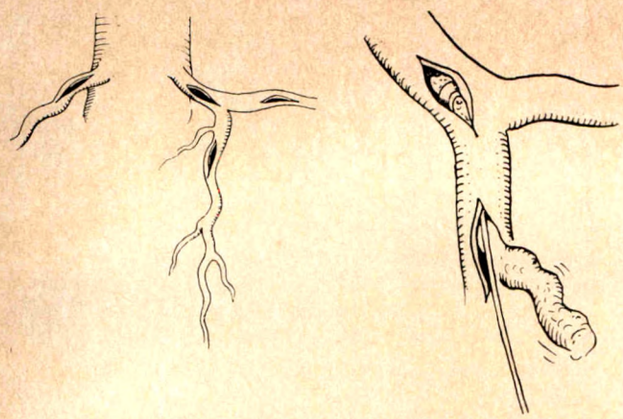

FIGURE 1. Method of performance of coronary endarterectomy. Reproduced with permission of the authors and publisher.[1]

surviving 30 minutes of occlusion, 71% developed ventricular fibrillation (VF) immediately *after* release of the artery, while only 28% of the 330 dogs developed VF *during* the occlusion. The reestablishment of blood flow to an area of myocardium made ischemic thus was more likely to precipitate VF than was the period of ischemia itself. Of course, these dogs previously had normal coronary arteries. Humans with AMI from severe coronary atherosclerosis who have early reestablishment of blood flow to ischemic or necrotic myocardium do not appear to have increased likelihood of development of VF.

Paul Klemperer,[8] who had done much to characterize the various collagen diseases, provided a scholarly historical piece entitled, "The History of Coronary Sclerosis." Why it took so long to connect myocardial infarction to the coronary arteries is nicely explained.

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Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. Am J Cardiol 1984;53:900–915.

Chapter in Book: Cabot RC, White PD, Taussig HB, Levine SA, Wood P, Friedberg CK, Nadas AS, Hurst JW, Braunwald E. How to write cardiologic textbooks. In: Hope JA, ed. A Treatise on Disease of the Heart and Great Vessels. London: Yorke Medical Books, 1984;175–200.

Book: Carrel A, Cutler EC, Gross RE, Blalock A, Craffoord C, Brock RC, Bailey CP, DeBakey ME. The Closing of Holes, Replacing of Valves and Inserting of Pipes, or How Cardiovascular Surgeons Deal with Knives, Knaves and Knots. New York: Yorke University Press, 1984:903.

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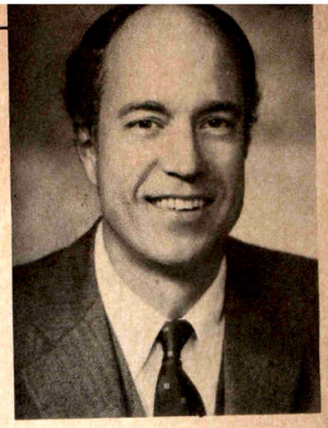

A Suggestion to Lighten the Load of Manuscript Reviewing

One of the most unselfish acts performed by productive members of the medical academic community is the reviewing of manuscripts submitted for publication by others. The time devoted to this task can be considerable, particularly so for the more prominent members of academia. Many leaders of academia are on the boards of several medical journals simultaneously—not because their names add prestige to the journal, but because they are wise and prompt reviewers whose counsel is widely sought. But reviewing manuscripts takes time away from their own tasks and too much energy expended on others subtracts time devoted to their own creative efforts.

An unfortunate principle of the peer-review process is that the best manuscripts receive the fewest reviews and the worst manuscripts receive the most reviews. The best manuscripts are usually accepted by the first journal to which they are sent. Therefore, they receive 1 to 3 reviews, depending on the policy of the particular journal; the manuscript usually is revised to varying degrees, and then accepted. The process for the less-than-superb or the inferior manuscript is not so rapid. The first journal to which the manuscript is sent may acquire 2 reviews for it, and when neither reviewer recommends acceptance and the editor agrees, the manuscript with the reviews is returned to the submitting author. Then the latter usually submits the manuscript to another journal, ideally after having revised the manuscript as suggested by the reviewers from the first submission. The editor of the journal receiving the previously rejected manuscript then sends it to 2 more reviewers—on occasion, to one who happened to have reviewed the manuscript for the first journal. These reviewers in turn often also provide unfavorable recommendations for the manuscript. The editor then returns the rejected manuscript to the authors, who in turn send it to another journal with or without additional revisions. The duplication process continues.

To prevent this depletion of reviewers' energies and also to prevent further publication delay, I suggest to authors who submit a manuscript rejected by another journal to the AJC that the authors enclose copies of all reviews from the previous journal, a copy of the original manuscript, 3 copies of the revised manuscript, and a response to all items raised by all reviewers from the previous journal. In other words, the response to the reviews from the previous journal should be identical to the response given reviews had they been sent from the AJC. This procedure might allow the AJC editor to make a rapid accept or reject decision on the manuscript, or it might allow him to send the manuscript for reexamination to only 1 reviewer rather than 2. The editor may choose to enclose the reviews from the previous journals' reviewers with the revised manuscript for the new reviewer.

I would welcome a thorough evaluation of this time-saving process and I will do my best not to be offended because the manuscript had not been sent initially to the AJC. I also urge other editors of cardiovascular journals to adopt the same procedure, because all 4 major USA cardiovascular journals essentially use the same pool of reviewers. The concept needs full testing so that the energies for reviewing will be conserved and those energies expended will be utilized more effectively and efficiently.

William C. Roberts

William C. Roberts, MD
Editor-in-Chief

VENTRICULAR FIBRILLATION DURING CORONARY ARTERIOGRAPHY

Nishimura et al[1] recently reported clinical findings in 39 patients who had ventricular tachycardia or ventricular fibrillation (VF) during coronary arteriography. At St. Lukes Hospital in New York, we undertook a similar study[2] in which we reviewed the records of 66 consecutive patients (1.7% of 3,906 undergoing angiography) who had 69 episodes of contrast-induced VF. In agreement with Nishimura et al,[1] we found few patients with normal coronary arteries (27%), an ejection fraction that was typically normal, a 1.5-times expected frequency of VF after right-sided injections and a wide range of heart rates immediately preceding the arrhythmia.[2] However, we also noted a strong statistical association between temporary right ventricular pacemaker use and the occurrence of VF.[2] We hypothesized that mechanically stimulated ventricular extrasystoles in the setting of a contrast material–induced increase in ventricular vulnerability,[3] at least in some cases, could have accounted for this association. Temporary pacemaker use at our institution is now avoided and the incidence of VF has decreased. It would be of interest to know whether Nishimura et al[1] have data relevant to this issue.

The relation between injection number and occurrence of VF deserves elaboration. As shown in Figure 1, we found that the frequency of VF peaks at the fourth left versus the second right coronary injection. This observation suggests a cumulative effect on the myocardium of Renografin® toxicity; the relatively greater "resistance" to VF during injections of the left coronary artery may relate to a greater degree of dye-dilution in that artery or to the higher left VF threshold.[4]

Finally, the role of Renografin-induced hypocalcemia (via chelation) in prolonging the QT interval deserves mention as an important factor contributing to electrophysiologic instability during coronary arteriography.[3,5,6]

Michael H. Lehmann, MD
Milwaukee, Wisconsin
19 July 1984

1. **Nishimura RA, Holmes DR, McFarland TM, Smith HC, Bove AA.** Ventricular arrhythmias during coronary angiography in patients with angina pectoris or chest pain syndromes. Am J Cardiol 1984;53:1496–1499.
2. **Lehmann MH, Cameron A, Kemp HG.** Increased risk of ventricular fibrillation associated with temporary pacemaker use during coronary arteriography. PACE 1983;6:923–929.
3. **Lehmann MH, Case RB.** Reduced human ventricular fibrillation threshold associated with contrast-induced Q-T prolongation. J Electrocardiol 1983;16:105–110.
4. **Horowitz LN, Spear JF, Josephson ME, Kastor JA, Moore EN.** The effects of coronary artery disease on the ventricular fibrillation threshold in man. Circulation 1979;60:792–797.
5. **Murdock DE, Euler DE, Scanlon PJ, Gunnar RM.** Electrophysiologic effects of intracoronary Renografin-76 (abstr). JACC 1983;1:729.
6. **Thomson KR, Violante MR, Kenyon T, Fischer HW.** Reduction in ventricular fibrillation using calcium-enriched Renografin-76. Invest Radiol 1978;13:238–240.

REPLY: The corroborative data presented by Murdock et al and Lehmann provide valuable additional information to our data on ventricular arrhythmias during coronary angiography. They raised the question of an increased incidence of VF during coronary artery bypass graft angiography. They postulate the relation between the relatively large volume of contrast material injected through the graft compared with the mass of perfused myocardium. We would add that grafts supply diseased coronary arteries and often supply blood flow to myocardium with previous ischemic damage. These 2 additional features increase the potential for VF during graft injection. The point of the specific contrast agent used is important. The use of contrast agents without EDTA and sodium citrate may reduce the potential for ventricular arrhythmias. The eventual use of newer, nonionic media may result in a further decrease in the incidence of ventricular arrhythmias.

The information presented by Lehmann is also important. In his study, right ventricular temporary pacing was associated with an increased occurrence of VF. We do not routinely place temporary pacemakers prophylactically, and therefore cannot comment on this factor in our patients. We agree that there may be a cumulative effect of contrast in some patients. In others, there may be both a balance of contrast toxic effects and ischemia. The role of Renografin-induced bradycardia and increased QT-interval prolongation may also be important. It is difficult to analyze the relation of each. We do feel that these postulates and the findings of Lehmann, Murdock, and ourselves, do point out the necessity to allow sufficient time between coronary injections to prevent cumulative toxic effects.

Rick A. Nishimura, MD
David R. Holmes, Jr, MD
Alfred A, Bove, MD
Hugh C. Smith, MD
Rochester, Minnesota
20 August 1984

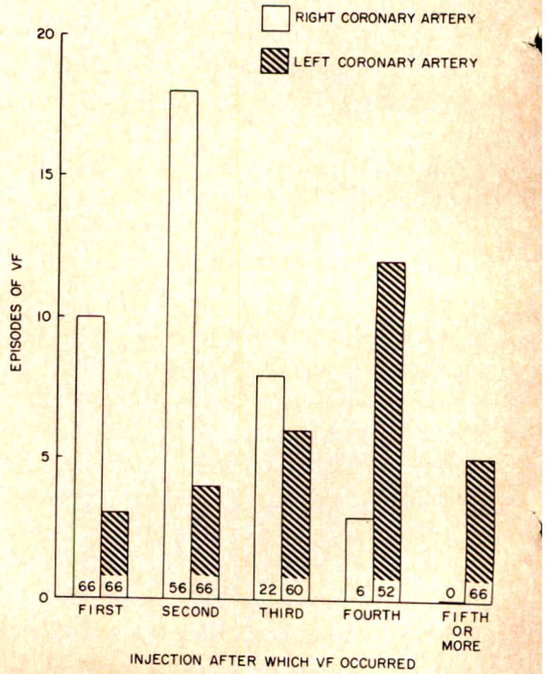

FIGURE 1. Occurrence of ventricular fibrillation (VF) according to number of contrast injections. Differences between distributions for right and left coronary arteries are statistically significant ($p < 0.05$). **Numbers** at **bottom** of **bars** indicate total corresponding injections for the entire study group of 66 patients.

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CHARACTERIZATION OF VENTRICULAR FIBRILLATION DURING CORONARY ANGIOGRAPHY

Although ventricular fibrillation (VF) is a well recognized complication of coronary angiography (CA), the clinical and electrocardiographic features of patients who have this complication have received little attention. Thus, the recent investigation by Nishimura et al[1] of 39 patients who have ventricular tachycardia or VF during CA is a welcomed analysis of this complication. We recently completed a similar study involving 8,081 patients in which 63 patients had 68 episodes of VF during CA. Our findings extend on the observations made by these investigators.

We also found that the total number of VF episodes was highest after right coronary artery (RCA) injection (33 of 68), followed by left coronary artery (LCA) injection (21 of 68) and coronary bypass graft injection (14 of 68). However, because only 636 of 8,081 patients undergoing CA had previous aortocoronary bypass surgery, the incidence of VF during bypass graft angiography was 2.2%, which was over 5 times that of an RCA injection (0.41%) and almost 10 times that of an LCA injection (0.25%) ($p < 0.001$). Five of the 39 episodes reported by Nishimura et al[1] followed a bypass graft injection. Although they did not indicate the incidence of VF in the various arteries, considering the relatively small portion of patients in which CA includes bypass graft angiography in most centers, we would suspect that they also had an inordinately high incidence of VF during bypass graft angiography. This observation may be important because the number of patients undergoing CA after bypass surgery will increase in the future. The high incidence of VF after bypass graft injection may result from the relatively large volume of contrast material injected per mass of perfused myocardium. We would also offer this as a possible explanation for VF occurring more often after RCA than after LCA injection.

We also frequently observed some degree of bradycardia before the onset of VF. However, marked bradycardia (≥50% increase in cycle length) preceded VF in only 9% of episodes. Because a similar incidence of bradycardia was also observed in 63 randomly selected patients who did not have fibrillation, bradycardia was not a useful predictor of VF in our study. However, patients in whom bradycardia did precede VF provide some insight into the possible mechanisms involved by suggesting that enhanced automaticity is an unlikely mechanism for the initiation of VF.

Comparing the 63 patients who had VF with 63 randomly selected patients not having VF during CA, we also found no difference with respect to history of arrhythmias, prior myocardial infarction, use of antiarrhythmic agents, age, baseline QT intervals, extent of coronary artery disease or ejection fraction. Thus, we could not identify any clinical feature that would predict the occurrence of VF.

Finally, VF is a direct result of the electrophysiologic effects produced by contrast media.[2–6] All patients in our study and in the study reported by Nishimura et al[1] underwent CA in which Renografin-76® was used as the contrast medium. Considerable experimental animal data indicate that the EDTA and sodium citrate in Renografin-76 may be contributing to this complication.[4–6] If the same holds true for the clinical situation, the incidence of VF during CA may be significantly reduced by using contrast media lacking these additives.

David K. Murdock, MD
Christine E. Lawless, MD
Henry S. Loeb, MD
John G. Furiasse, MD
Steven Pagano, MD
Patrick J. Scanlon, MD
Hines, Illinois
13 July 1984

1. **Nishimura RA, Holmes DR, McFarland TM, Smith HC, Bove AA.** Ventricular arrhythmias during coronary angiography in patients with angina pectoris or chest pain syndrome. Am J Cardiol 1984;53:1496–1499.
2. **Murdock DK, Euler DE, Scanlon PJ, Gunnar RM.** Mechanisms responsible for ventricular fibrillation during coronary angiography (abstr). Circulation 1983;68(3):147.
3. **Poplo KA, Ross AM, Onaven JM, Ingram JT.** Identification and description of separate mechanisms for two components of renografin cardiotoxicity. Circulation 1978;58:520–528.
4. **Murdock DK, Euler DE, Kozeny G, Murdock JD, Scanlon PJ, Loeb HS.** Ventricular fibrillation during coronary angiography: the role of calcium binding additives. Am J Cardiol 1984;54:897–901.
5. **Thomson KR, Violante MR, Kenyon T, Fischer H.** Reduction of ventricular fibrillation using calcium-enriched Renografin 76. Invest Radiol 1978;13:238–240.
6. **Violante MR, Thomson KR, Fischer HW, Kenyon T.** Ventricular fibrillation from diatrizoate with and without chelating agents. Radiology 1978;128:497–498.

CHEST THUMP ACCELERATION OF VENTRICULAR TACHYCARDIA

I read the report of Krijne[1] on rate acceleration of ventricular tachycardia (VT) after a precordial chest thump. We[2] previously reported 3 patients who had acceleration of VT after a chest thump. All 3 patients were receiving oral digoxin with drug levels above normal at the time of the acceleration of VT. When digoxin was withheld, chest thump successfully terminated further episodes of VT in 2 patients and did not affect the VT in the remaining third patient; however, the phenomenon of VT acceleration was not observed.

Samuel Sclarovsky, MD
Petah-Tikva, Israel
24 July 1984

1. **Krijne R.** Rate acceleration of ventricular tachycardia after a precordial chest thump (abstr). Am J Cardiol 1984;53:964.
2. **Sclarovsky S, Kracoff OH, Agmon J.** Acceleration of ventricular tachycardia induced by a chest thump. Chest 1981;80:596–599.

CORONARY ARTERY SURGERY STUDY

The editorial titled "The Coronary Artery Surgery Study (CASS): Do the Results Apply to Your Patient?" by Roberts and Manning[1] perpetuates a misconception about the validity of the CASS results despite nonadherence to protocol by more than 25% of the medically assigned patients. This misunderstanding has arisen as a result of a quotation from the CASS report that was taken out of context: "Analyses of CASS mortality data by treatment received and by means of censoring at the time of crossover do not change the results."[2] The next sentence, however, was omitted: "These analyses are not reported since they are of dubious scientific merit in the context of a randomized trial."[2] (emphasis added). The authors of the CASS further stated that, "Given the observed degree of noncompliance to treatment assignment, CASS cannot definitively test the true contrast in outcome between medical and surgical therapy . . . ."[2] If patients deviate from an experimental protocol, they seriously jeopardize the validity of a study. The data may not be simply "reshuffled" and reinterpreted without destroying the randomized nature of the study.

The "intention to treat" principle is a well-established and useful statistical convention, but it should not be used to give legitimacy to studies that may be fatally flawed by nonadherence to the experimental protocol. The policy of analyzing all randomized subjects in the groups to which they were originally assigned ("intention to treat") reduces the risk that a therapeutic benefit will be claimed when none exists. However, the effect of the therapy may be diluted by noncompliant subjects, so that the sensitivity or ability to detect a real difference due to treatment, will be reduced.[3]

Peto et al[4] pointed out that the ability of a clinical study to distinguish between the merits of 2 treatments depends on how many patients die, rather than on the number of patients entered into the study. Suppose, for example, that coronary bypass surgery could prevent as many as 33% of the deaths that would occur in the nonsurgical group. To have only an even chance of demonstrating this fact, we would need to observe 100 deaths; to be safe, the trial should involve, perhaps, 200 deaths. Because the CASS reported only 65 deaths (29 surgical and 36 medical), the observed improvement in survival in the surgical group failed to reach statistical significance. Given the number of deaths in the CASS, there was a low probability that the benefit of coronary artery bypass could be demonstrated.

Gerald S. Weinstein, MD
New York, New York
8 August 1984

1. **Roberts WC, Manning DM.** The Coronary Artery Surgery Study (CASS): do the results apply to your patient? Am J Cardiol 1984;54:440–443.
2. CASS principal investigators and their associates: Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery bypass surgery: survival data. Circulation 1983;68:939–950.
3. **May GS, DeMets DL, Friedman LM, Furberg C, Passamani E.** The randomized clinical trial: bias in analysis. Circulation 1981;64:669–673.
4. **Peto R, Pike MC, Armitage A, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG.** Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585–612.

REPLY: The letter by Weinstein is misleading. In the first paragraph, Weinstein indicates that nonadherence to protocol occurred in over 35% of patients. This is incorrect. The author added together the noncompliance rate in the surgical and in the medically assigned patients to arrive at the

figure of 35%. In actuality, the noncompliance rate is only 17%, i.e., the average of the 11% in the 390 surgical patients and 23.5% in the 390 medical patients. The "intention to treat" approach analyzes the policy or strategy of planned surgical treatment versus the policy or strategy of planned medical treatment. The CASS was never designed as an efficacy study, and any attempt to analyze the data in that way would have been inappropriate.

Weinstein properly points out that in a clinical trial that uses mortality as an endpoint, it is the number of patients who die that ultimately determines the sample size. When there is a clinically meaningful divergence in survival curves between 2 treatment groups, one needs sufficient numbers to prove statistical significance. However, when the 2 survival curves are essentially the same, as was the case in the CASS, then what is the clinical meaning of a minor difference regardless of the numbers used? For example, I do not believe that clinicians would be impressed by a 2% reduction in mortality even if it were statistically significant with 10,000 patients enrolled. Generally, a 20 to 25% reduction in mortality is required to convince physicians of the advantage of a new treatment (e.g., BHAT); the existing CASS data suggests that a 20 to 25% mortality reduction could have not been achieved regardless of the numbers used.

Arthur J. Moss, MD
Rochester, New York
6 September 1984

REPLY: The CASS assessed the long-term benefit of surgical revascularization of the myocardium regarding myocardial infarction (MI) occurrence and survival in patients with mild angina (with or without a prior MI) and in patients who had recovered from a MI without symptoms. After 5.5 years of follow-up there was no significant difference in survival rates or occurrence of MI in those randomized to surgery compared with those randomized to medical treatment. However, there was a greater improvement in symptoms and function in the surgical group. It was concluded from this that surgery can be deferred until symptoms become a problem for the patients despite medical treatment.

Those in the randomized study were a highly selected subgroup of patients with angina or MI; only 5% of those originally screened entered the study. Angiographically normal (or minimal coronary artery disease [CAD]) patients were excluded. Also eliminated were those with severe CAD not suitable for grafting (4.9%). Those with severe angina (36.5%) or left main CAD (found in only 4.3% of 16,000 subjects) were also excluded.

Roberts and Manning conclude from these findings that even coronary angiography should be *avoided* unless symptoms worsen and surgery would be seriously considered on that basis. Weinstein claims that there is a misconception about the CASS findings engendered by a large degree of noncompliance to assigned treatment. However, the study of "randomizable" subjects would appear to reassure on that point, but only if the findings were positive. Weinstein is correct in his assertion that deviation from the experimental protocol does call into question the validity of the study. Subgroup analysis is hazardous if the study was not originally designed to examine these issues. The "intention to treat" principle cannot fully compensate for major nonadherence to the experimental protocol. The bias in the analysis of all randomized subjects keeping them in their originally assigned groups (intention to treat) does minimize the danger of claiming a therapeutic benefit when none exists. But as Weinstein asserts, the effect of therapy can be seriously underestimated by this practice if there is a large amount of crossover or noncompliance.

I agree with Weinstein that the number of events was probably too few to establish a modest difference in survival. In any event, the noncompliance makes a claim of no difference difficult to accept. Only a sizable and significant *difference* would be credible under the circumstances, since this would be a minimal estimate of the effect. The study was not large enough to demonstrate a 50% reduction in the death rate with a better than even chance of this being on the basis of sampling variation. Only a 67% reduction in mortality could be reliably detected (with 0.8 probability). If the actual difference found, whether statistically significant or not, is trivial the issue is moot. There is little virtue in enlarging such a trial to reliably detect differences so small that they would not matter anyway.

We must examine this surgical trial in the context of the epidemiologic perspective on the way coronary artery disease evolves in the general population. This indicates that we must diagnose this disease on its way to happening and correct predisposing factors before the first symptom appears. The first prolonged attack of ischemic chest pain carries a 33% fatality rate and half of all CAD deaths are sudden. One in 6 coronary attacks present with sudden death as the first, last and only symptom. For these, only a preventive approach can be of help.

We do continue to have many CAD patients who have managed to survive MI or have stable angina pectoris. Their outlook, on average, is grim in regard to risk of recurrent MI, cardiac failure, stroke and survival. At this point, when CAD becomes clinically manifest, we are dealing with advanced 2- or 3-vessel CAD and a damaged myocardium. Because we are then dealing with a completed catastrophe, the severity of the CAD at the time of the diagnosis is the chief determinant of the patients' outlook. The standard risk factors at this point have little short-term effect. One risk factor is applicable. Seven studies have shown that quitting cigarette smoking reduces post-MI mortality by 20 to 50%, a result that rivals cardiac surgery or medical treatment. One noteworthy finding of CASS was that 3 of 4 of the 40% of patients who were smoking cigarettes when they entered the trial continued to smoke. Perhaps we should compare medical and surgical treatment with quitting cigarette smoking.

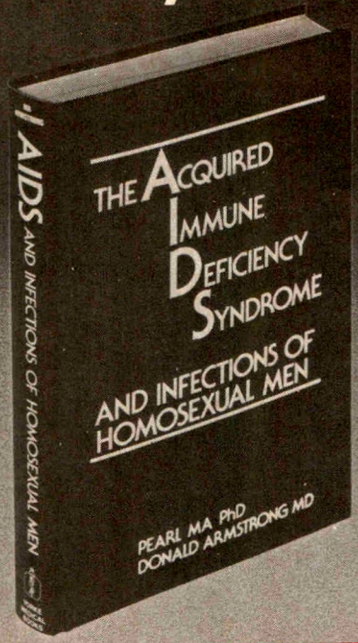
It appears unlikely that surgery alone can restore the damaged myocardium to full function or slow the progression of CAD in patients with angina or a healed MI. The CASS trial suggests that with the advent of better medical treatment, including β-blocking drugs, aspirin and calcium channel-blocking drugs, we can get better results than formerly with respect to both relief of symptoms and survival on medical treatment. What this study may be showing is that bypass surgery is now no better than recently improved medical treatment. Hence we may return to the previously held indications for surgery: angina that the patient cannot tolerate because of life style, personality, inconvenience, or adverse effects from medication. The chief benefit promised is improvement of exercise tolerance and relief of symptoms, but not lengthening of life over medical treatment.

CASS was carried out over a period when CAD mortality in the U.S. was decreasing. The good prognosis of those medically treated was the most noteworthy finding. With modern medical treatment the MI rate was only 2.2% and the mortality rate only 1.6% per year. This may not be entirely due to better treatment, because the decline has not occurred in many European countries with equally sophisticated medical care. Surgical therapy offered no advantage in returning patients to work or in improving their recreational activity. This calls into question surgical indications of rehabilitation and return to work.

William B. Kannel, MD
Boston, Massachusetts
17 October 1984

AIDS

An important new book on today's most virulent epidemic



From the Publishers of The American Journal of Medicine, The American Journal of Surgery, and Cutis

Acquired Immune Deficiency Syndrome (AIDS) and Infections of Homosexual Men

edited by **Pearl Ma, PhD,** and **Donald Armstrong, MD** with a foreword by **David J. Sencer, MD,** *Commissioner of Health, New York City; formerly Director, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services*

0-914316-38-9, 442 pages, illus., January 1984, $39.50

The first scientific presentation to review all the facts in full

AIDS has become one of the most publicized diseases in modern times. It has produced fear and confusion in the general public and presented a formidable challenge to the medical community. Physicians and scientists have begun work on managing this epidemic, disease control centers continue to search for answers, and the federal government has declared AIDS the number one health priority of the nation. Understanding this disease demands cooperation between many different medical specialties, and papers on this subject have been published in many diverse journals not regularly read by individual specialists. Now, for the first time, two highly distinguished medical experts, Drs. Pearl Ma and Donald Armstrong, have coordinated in one easily accessible volume the complete range of interdisciplinary approaches to this complex disease, with contributions by the most eminent researchers and physicians in disease control and hospital teaching centers throughout the country. Comprehensive coverage is given to the entire spectrum of sexually transmitted diseases, and an additional section on diagnostic perspectives offers never before published material on why this syndrome occurs primarily among homosexual men. For any physician or other health care professional interested in the prevention and cure of this modern epidemic, this book is an indispensable guide to recognizing and treating AIDS and other sexually transmitted diseases.

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W. Lawrence Drew, MD
Lewis M. Drusin, MD
Yehudi M. Felman, MD
Donald P. Francis, MD
Jan Gerstoft, MD
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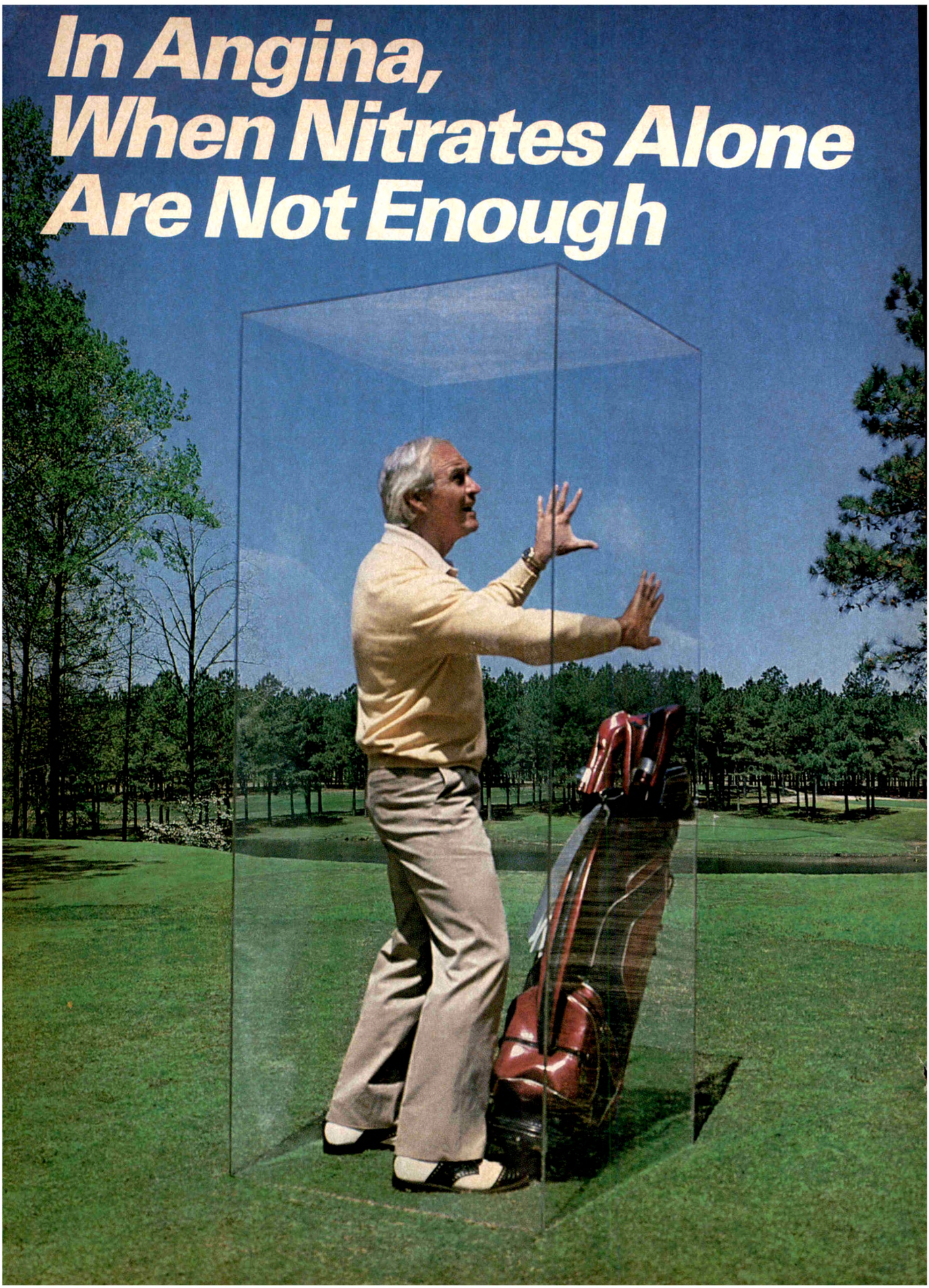
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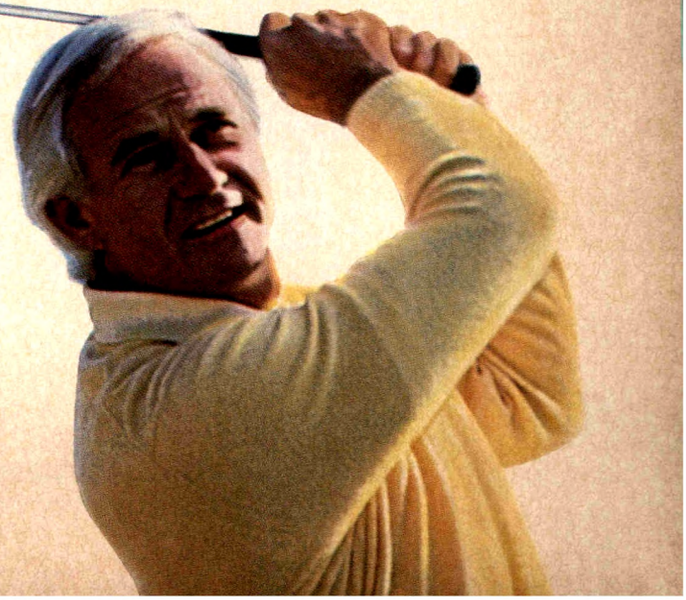

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block.

Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension, usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Elevations of liver enzymes have been reported. Four cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR <50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in less than 0.5% of patients, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions, spotty menstruation, ecchymosis, bruising, gynecomastia, and psychotic symptoms. Overall continuation rate was 94.5% in 1,166 patients.

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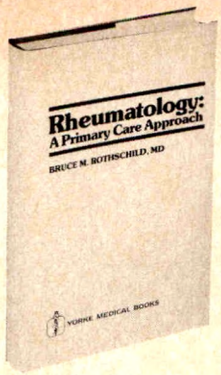

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Bruce M. Rothschild, MD

Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V.A. Medical Center North Chicago, Illinois

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Abbreviated Table of Contents

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Section 2 **Patterns**
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Digoxin therapy with tablets may be compromised by:

☐ many commonly coadministered drugs, eg, antibiotics, antidiarrheals, antacids, and agents that increase or decrease gut motility

☐ concurrent GI disease: diarrhea, malabsorption syndromes, intestinal diseases, constipation

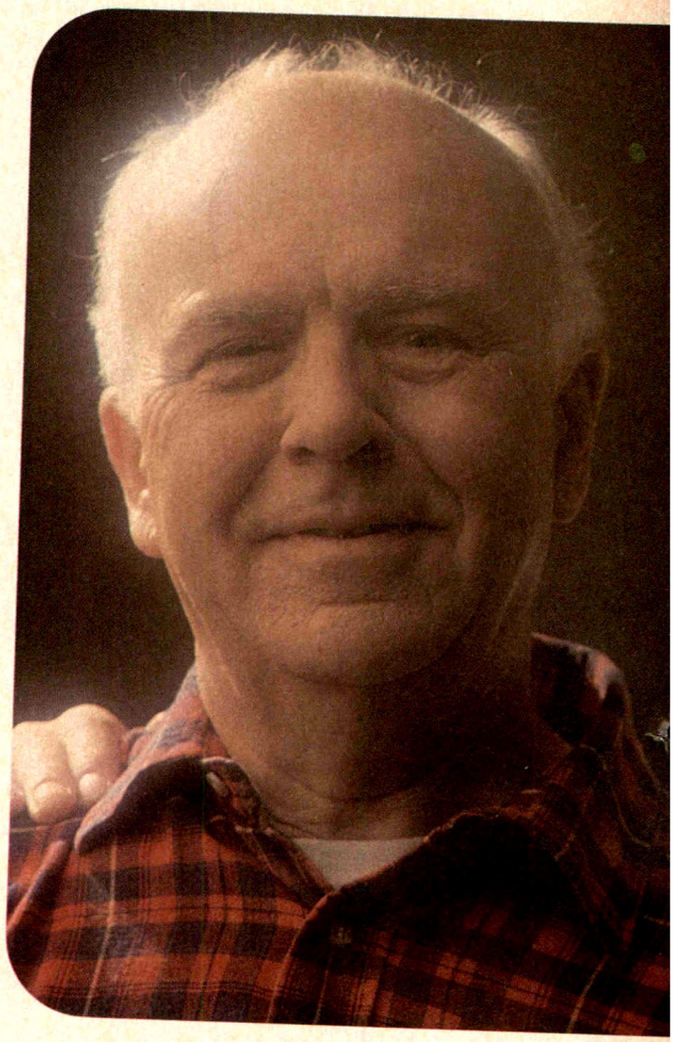
Digoxin therapy with Lanoxicaps® (digoxin solution in capsules) allows the digoxin to be much more rapidly and completely absorbed. Whereas tablet bioavailability is only in the range of 60% to 80%, bioavailability with Lanoxicaps is similar to that following IV administration, 90% to 100%. *Less variability in the amount of digoxin absorbed means less risk of over- or under-digitalization, improving your patient's safety margin.*

"Bioavailability of digoxin has represented one of the most discussed topics of cardiovascular pharmacology of the past decade. The consequent changes in pharmaceutical manufacturing have led to preparations with nearly optimal bioavailability thus favouring a substantial advancement towards a safer treatment."

Levy G, cited by Malini PL, Strocchi E, Negroni S, et al: Greater bioavailability of digoxin in a new capsule preparation. *Current Therapeutic Research* 1983;33:646-650.

"Data collected so far show that if a product is fully bioavailable, the bioavailability in different subjects and in the same subject at different times is within a very narrow range, say 95—100%. However, if a poorly available product has an *average* bioavailability of say 50%, the range in individual patients, and in the same patient at different times, covers a tremendous range, sometimes from 0 to 100%!"

Wagner JG: An overview of the analysis and interpretation of bioavailability studies in man. *Pharmacology* 1972;8:102-117.



The new standard in digoxin

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Please see brief summary of prescribing information on following page.

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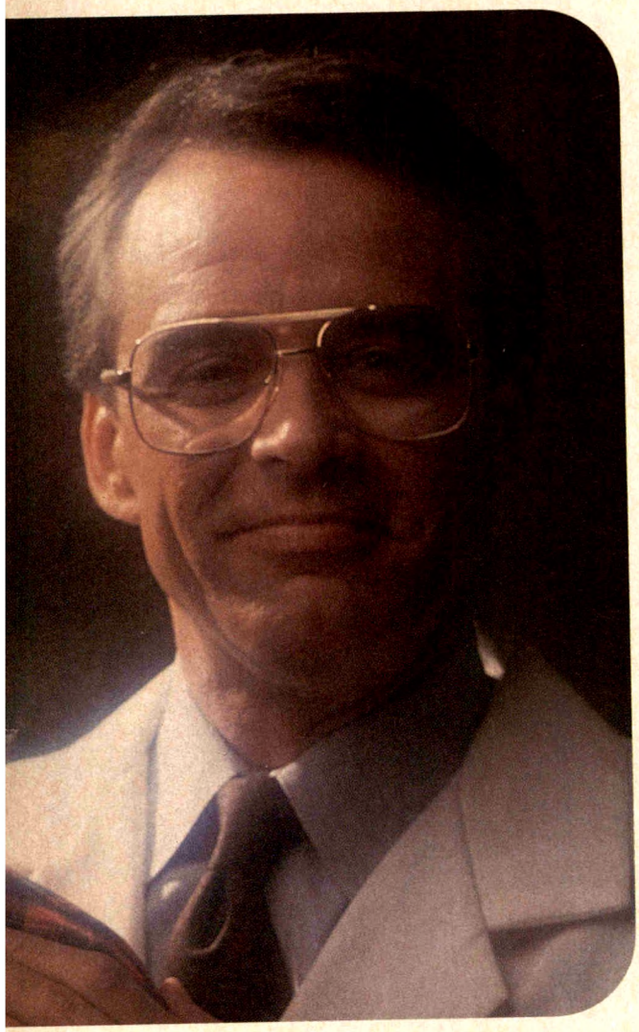


"The enhanced bioavailability of the capsule formulation and the resulting minimized intersubject and intrasubject variability in serum digoxin concentrations make the capsule dosage form the preferred form of oral digoxin for use in patients who typically have a multitude of factors that can markedly alter digoxin bioavailability."

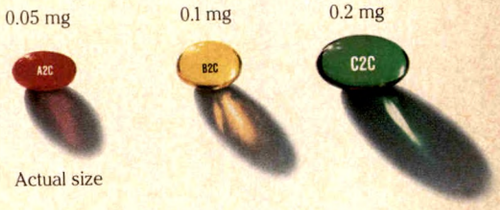
Johnson BF: Influences of dosage form and other factors on variability in digoxin absorption, in *Digoxin Therapy: The Role of Lanoxicaps®*. Burroughs Wellcome Co., 1983, pp 14-19.

"The more incompletely a drug is absorbed, the more will its absorption vary between patients and in the same patient with time. Drug formulation should always strive for the most complete bioavailability ...."

Koch-Weser J: Drug therapy: Bioavailability of drugs (second of two parts). *N Engl J Med* 1974;291:503-506.

Monograph Available

To receive a compilation of clinical studies, entitled *Digoxin Therapy: The Role of Lanoxicaps®*, just ask your B.W. Co.® representative or write: Lanoxicaps Monograph, Burroughs Wellcome Co., Research Triangle Park, NC 27709.



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(digoxin solution in capsules)

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Brief Summary of Prescribing Information

Before using Lanoxicaps® (digoxin solution in capsules), the physician should be thoroughly familiar with the basic pharmacology of this drug as well as its drug interactions and its indications and usage.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in ventricular fibrillation. Any untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS: The use of digoxin or other digitalis glycosides in the treatment of obesity is unwarranted and dangerous.

It is recommended that digoxin in soft capsules be administered in divided daily doses to minimize any potential adverse reactions. Where compliance is considered a problem, single daily dosing may be appropriate (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in complete prescribing information). More time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range", because potassium depletion sensitizes the myocardium to digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section in complete prescribing information).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Hypocalcemia can nullify the effects of digoxin in man; digoxin may be ineffective until serum calcium is restored to normal.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine and verapamil cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized.

Certain antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the gut (see Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section in complete prescribing information). The magnitude of rise in serum digoxin concentration may be as much as two-fold in some cases. This interaction is significantly reduced if digoxin is given as Lanoxicaps.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sino-atrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias. *Quinidine* and *verapamil* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine* and certain *anticancer drugs* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias, because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% being considered serious (1 to 4% of patients receiving digoxin). Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage. Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances.

Gastrointestinal—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosage. Uncontrolled heart failure may also produce such symptoms.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, apathy and psychosis can occur.

Other—Gynecomastia is occasionally observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

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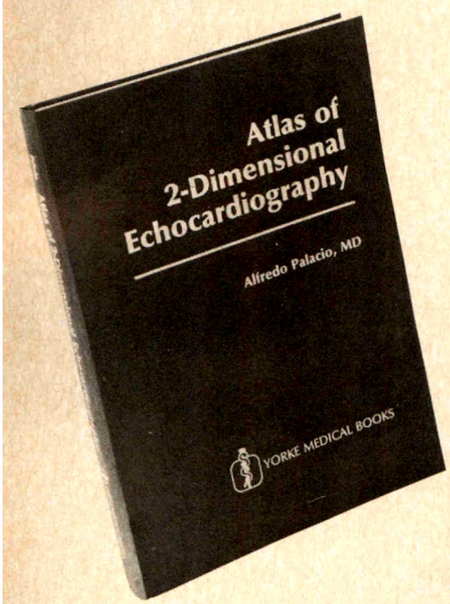

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Foreword by David H. Spodick, MD, DSc
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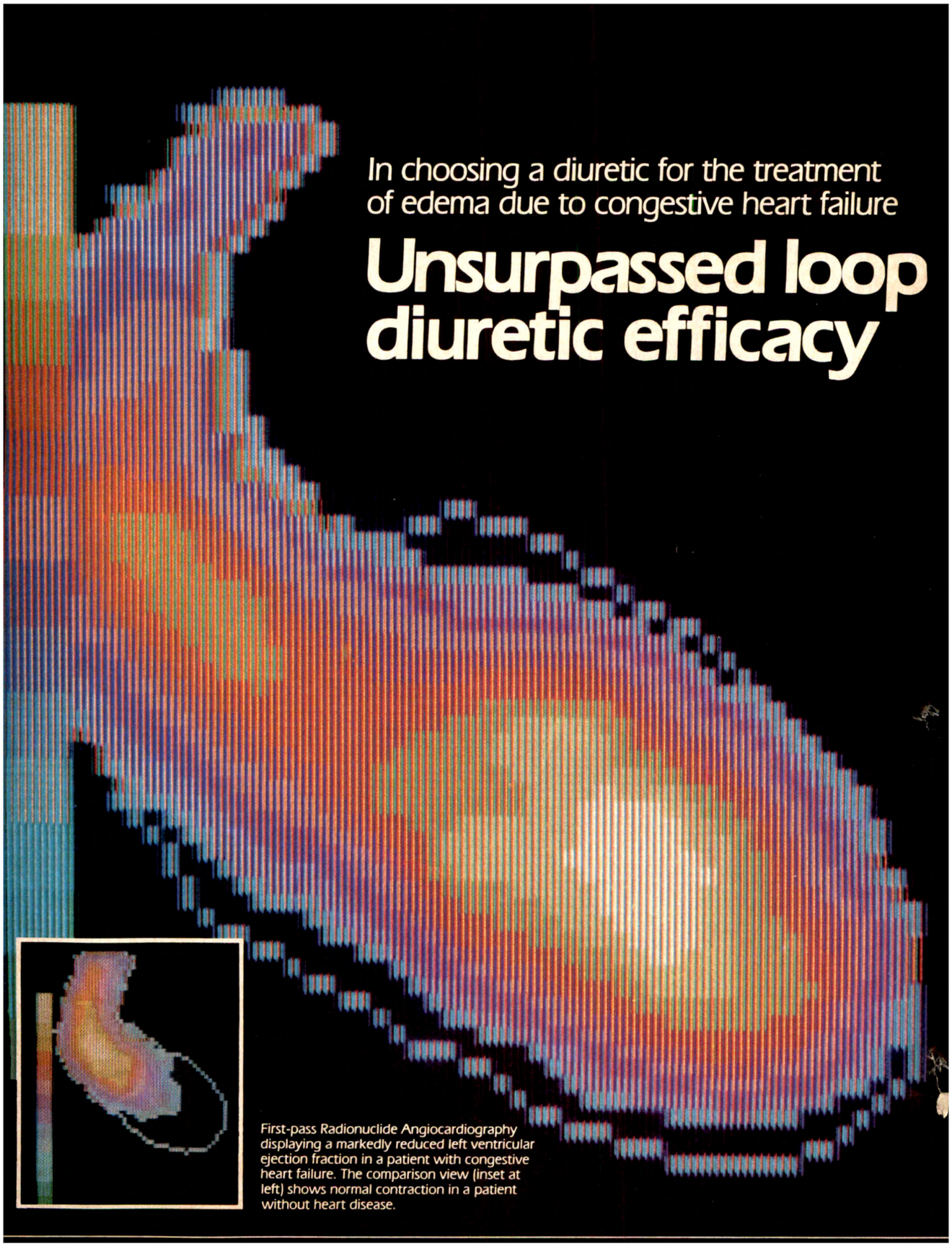


In choosing a diuretic for the treatment of edema due to congestive heart failure

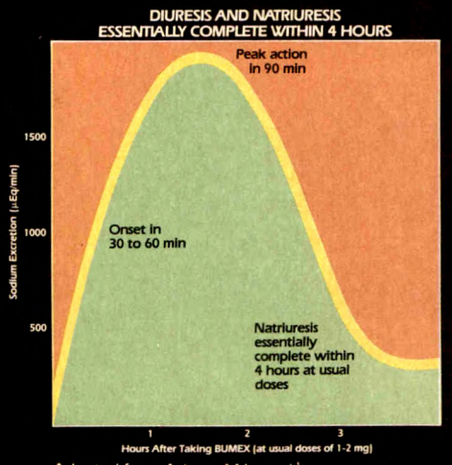
Unsurpassed loop diuretic efficacy

First-pass Radionuclide Angiocardiography displaying a markedly reduced left ventricular ejection fraction in a patient with congestive heart failure. The comparison view (inset at left) shows normal contraction in a patient without heart disease.

Diuresis essentially complete within 4 hours with Bumex at usual doses[1,2]

Faster completion of diuresis with unsurpassed efficacy: that's what makes Bumex easy to live with compared to other loop diuretics.

Bumex rapidly mobilizes a high volume of fluid and sodium in edematous patients with congestive heart failure.[3] And Bumex is unsurpassed in reducing edema and improving the functional status of CHF patients.[4,5]

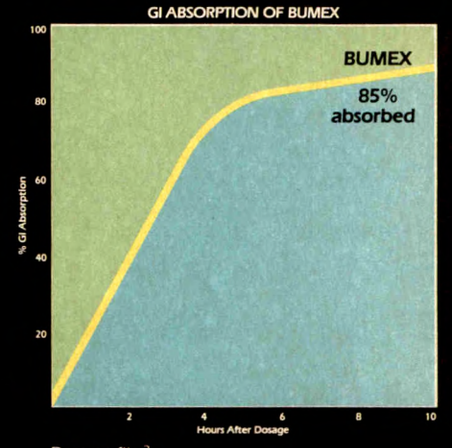


Adapted from Asbury MJ, *et al.*[1]

Effective diuresis through rapid, nearly complete absorption

Eighty-five percent of an oral dose of Bumex is absorbed through the GI tract;[3] thus the diuretic response you can expect with oral Bumex is almost equal in magnitude to the response you get with an I.V. dose.[3,6]

As with all loop diuretics, excessive doses of Bumex can lead to profound diuresis with water and electrolyte depletion, including hypokalemia. Serum electrolytes should be monitored periodically, especially in patients on low-salt diets or those treated for prolonged periods or on high doses.



Data on file.[3]

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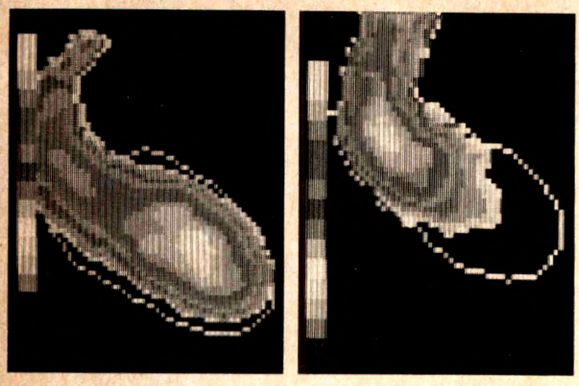
Faster completion of diuresis that's easier to live with

Faster completion of diuresis... that's easier to live with.



First-pass Radionuclide Angiocardiography displaying a markedly reduced left ventricular ejection fraction in a patient with congestive heart failure. The comparison view (on right) shows normal contraction in a patient without heart disease.

- Essentially completes diuresis within 4 hours, at usual doses
- Among loop diuretics, unsurpassed in volume of fluid and sodium excreted
- Unsurpassed in reducing edema and improving functional status
- Rapidly, nearly completely absorbed—for a predictable diuretic response
- Allows for early-evening diuresis—for days of normal activity, nights of uninterrupted sleep
- Contraindicated in anuria, markedly elevated BUN, hepatic coma and severe electrolyte deficiency
- The most frequent clinical adverse reactions considered probably or possibly related to Bumex are: muscle cramps, dizziness, hypotension, headache, nausea and encephalopathy.

References: 1. Asbury MJ, *et al: Br Med J 1:* 211-213, Jan 22, 1972. **2.** Davies DL, *et al: Clin Pharmacol Ther 15:*141-155, Feb 1974. **3.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **4.** Dixon DW, Barwolf-Gohlke C, Gunnar RM: *J Clin Pharmacol 21:*680-687, Nov-Dec 1981. **5.** Halstenson CE, Matzke GR: *Drug Intell Clin Pharm 17:*786-797, Nov 1983. **6.** Pentikäinen PJ, *et al: Br J Clin Pharmacol 4:*39-44, Jan 1977.

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Bumex (bumetanide/Roche) may increase urinary calcium excretion.
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Less frequent clinical adverse reactions are weakness, impaired hearing, rash, pruritus, hives, electrocardiogram changes, abdominal pain, arthritic pain, musculoskeletal pain and vomiting.
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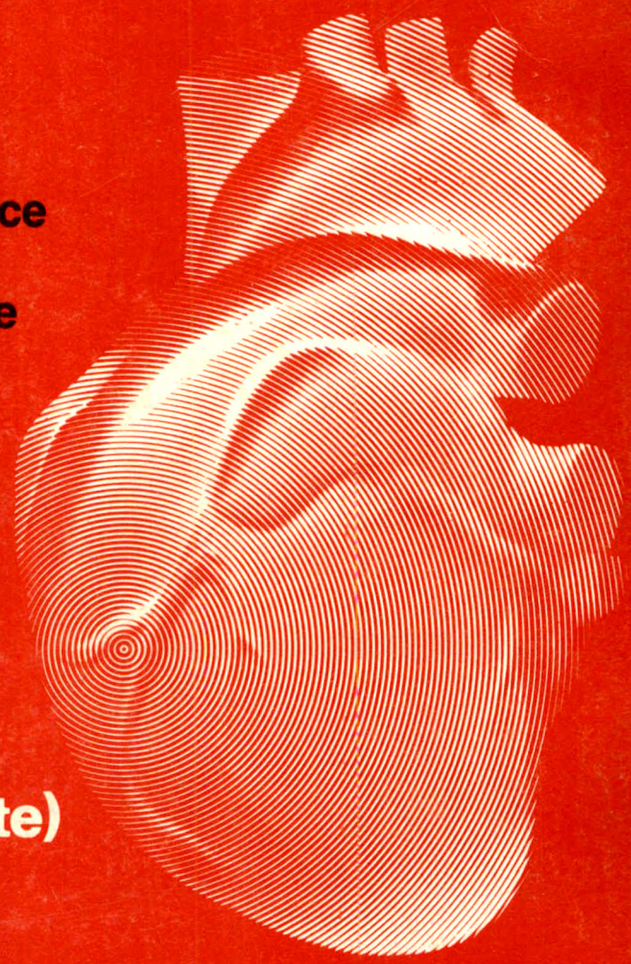

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New Concepts in the Mechanisms and Treatment of Congestive Heart Failure

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Professor of Medicine
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University of Minnesota
Minneapolis, Minnesota

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VOLUME 55

NUMBER 2

New Concepts in the Mechanisms and Treatment of Congestive Heart Failure

Introduction

JAY N. COHN, MD

Recent reawakening of interest in the syndrome of congestive heart failure (CHF) can be attributed to several factors:

(1) Sophisticated noninvasive and invasive techniques make quantitation of impaired left ventricular function more available than in the past.

(2) New pharmacologic approaches demonstrate the ability to produce striking augmentation of depressed ventricular function and thus are stimulating physicians to become more aggressive in the management of patients with CHF.

(3) Follow-up of patients with signs or symptoms of CHF reveals a far more grim prognosis for survival than previously suspected.

(4) More than a decade of extensive experience with coronary angiography and coronary artery bypass surgery reveals that left ventricular dysfunction may be the most important factor determining prognosis.

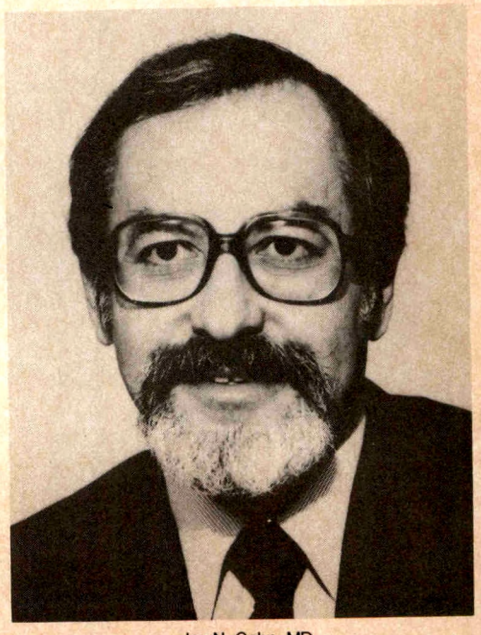
The burgeoning reports on pathophysiologic, clinical and therapeutic aspects of CHF and the wide array of therapeutic options now available for the management of the syndrome have placed a burden on the clinician to make complex management decisions in a rapidly changing environment. How should the severity of CHF be assessed? How can the prognosis be predicted? How aggressive should treatment be? Which drugs should be used and in which order? How can clinical response be monitored? The present symposium does not pretend to answer these substantive clinical questions; instead, it provides a framework within which the clinician may build an understanding of the syndrome and a rational approach to management.

From the Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota.

Address for reprints: Jay N. Cohn, MD, Box 488 Mayo, University of Minnesota, Minneapolis, Minnesota 55455.

McFate Smith opens the symposium with an analysis of data relating to the epidemiology of CHF. Despite generations of experience with this clinical syndrome, the absence of rigorous criteria for diagnosis and classification has hindered the collection of reliable information. Furthermore, the epidemiologic characteristics of the syndrome are probably changing as our population ages, as treatment for hypertension becomes more effective and as our ability to assess ventricular function more accurately becomes more widespread.

The pathophysiology of CHF is reviewed by William Parmley, who describes the role of various etiologic factors, changes in cardiac muscle and pump function,



Jay N. Cohn, MD

biochemical abnormalities, peripheral vascular alterations and therapeutic implications of this disturbed physiology. Gary Francis provides a scholarly review of the neurohumoral mechanisms that may contribute to inappropriate peripheral vasoconstriction in CHF. Rapid expansion of our understanding of the cellular mechanisms controlling activity of the sympathetic nervous system and of our insight into the abnormalities of neural control in CHF may someday contribute to new approaches to long-term management.

Use of quantitative exercise testing with measurement of respiratory gas exchange is a valuable tool in assessing the severity and monitoring the course of patients with CHF. Karl Weber and Joseph Janicki review their extensive experience with this method and provide physiologic background information that is important for understanding the usefulness and interpretation of such testing.

Therapeutic approaches to heart failure are considered by Barry Levine, Robert Cody and Edmund Sonnenblick. Levine addresses the use of vasodilators for reducing preload and impedance as a means of improving left ventricular pump function. Cody describes his studies with enalapril, a new converting-enzyme inhibitor that appears to produce a sustained improvement in cardiac function and exercise performance. Sonnenblick and associates review the concept behind the development of new inotropic drugs and discuss where such agents may fit in our overall schema for managing CHF.

The sketchy data available on the natural history and therapeutic efficacy of various interventions in CHF make it clear that additional well-controlled studies are urgently needed to place management of this common and lethal disorder on a more rational basis. The problems in designing such studies are reviewed in the paper by Curt Furberg and associates at the National Heart, Lung, and Blood Institute. Plans are under way to undertake a multicenter national study under NHLBI auspices to evaluate preventive and therapeutic aspects of CHF. Furberg's contribution describes the rationale for the planned approach. The multicenter Veterans Administration Cooperative Study (V-HEFT), scheduled for completion in 1985, may provide new insights into natural history and therapeutic responses that may help to answer some questions and is also likely to raise others.

CHF is a pathophysiologic entity of great heterogeneity. Prevention of progression of the syndrome rather than treatment of its end stage appears to be the more likely approach to be successful in altering its prognosis. But how to recognize the early stage of the syndrome and how to intervene are problems still to be resolved.

Epidemiology of Congestive Heart Failure

WILLIAM McFATE SMITH, MD

Despite the paucity of epidemiologic work on congestive heart failure (CHF), the salient features of the natural course of cardiac failure are understood. The estimated 1983 incidence of CHF in the United States was 214,000 men and 184,000 women. The estimate of prevalence was 2.3 million persons, with a remarkable increase with advancing age and higher rates in men than women at all ages. Overt heart disease plus age are the principal determinants of the incidence of CHF. Nearly 90% of patients with CHF have systemic hypertension or coronary heart disease, or both, as the antecedent underlying condition. Diabetes mellitus increases the risk of CHF at all ages, particularly in women and those treated with insulin. The prognosis after diagnosis of CHF is grim and is related to the degree of myocardial dysfunction. The challenge is to develop more effective drugs not only for the management of overt CHF, but also for the prevention of its progression. (Am J Cardiol 1985;55:3A–8A)

During the past 3 decades, the epidemiologic method has been increasingly applied to the search for the causes of the major chronic degenerative diseases. Systemic hypertension and atherosclerosis are perhaps the most notable examples. Congestive heart failure (CHF), of course, is not a disease, but "a pathophysiologic state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues."[1] Nonetheless, because the epidemiologic approach involves the assessment of the distribution pattern of *any* event of medical concern in populations, in accordance with some characteristic that is believed to influence the occurence of the event (e.g., age, sex, race, body type and antecedent medical history), it is appropriate to apply the epidemiologic method to understanding the causes and prognostic implications of cardiac failure.

Little epidemiologic study relating to CHF has been done, and virtually all studies before Framingham were hampered by the absence of uniform diagnostic criteria and differing observational methods applied under differing circumstances to different populations. The available mortality data, autopsy studies and morbidity data based on hospital statistics did not readily translate into community prevalence rates. Nonetheless, certain salient features of the natural course of cardiac failure were understood and projections of the magnitude of the problem in terms of prevalence and incidence were not grossly inaccurate. We are also certain that CHF is a common consequence of a variety of underlying causes. Moreover, despite modern management, CHF has a dismal prognosis, with only 50% of patients surviving 5 years after diagnosis.

From the Medical Research Institute of San Francisco, San Francisco, California.

Address for reprints: William McFate Smith, MD, Medical Research Institute of San Francisco, IEBM—Pacific Medical Center, 2200 Webster Street, San Francisco, California 94115.

Prevalence

Before the Framingham study, the best estimates of prevalence based on mortality rates varied from 0.05 to 2/1,000 per year. Clinical wisdom held that CHF was more frequent in the elderly patient and was the usual cause of death in heart disease. Morbidity estimates drawn from private practice and hospital wards led Paul Dudley White to conclude that CHF developed in more than half of all persons with organic heart disease. Klainer et al[2] reported that 1 to 2% of total admissions to selected hospitals in Australia, Canada and the United States were for cardiac failure. Community prevalence rates cannot be drawn from such data; however, in communities in which the population at risk is well defined, such rates give some indication of the prevalence of CHF serious enough to warrant hospitalization. Using the 1960 U.S. census data and such hospital statistics, it was suggested that 1% of the population had cardiac failure and that the admission rate for CHF was approximately 2/1,000 population per year (Table I). The hospital data also supported the clinical impression of a strong correlation of CHF with advancing age, with up to 80% of patients admitted in 2 series older than 60 years of age.

TABLE I Estimates of Period Prevalence of Cardiac Failure (Rates Per 1,000 Population, U.S.)

Source	Method	Period	Rate
Death certificates	Analysis of primary diagnosis	1 yr	0.05
Death certificates	Analysis of multiple diagnoses	1 yr	0.9
Death certificates	Estimates by expert cardiologists	1 yr	1.8
Autopsy reports	Estimate from autopsies	1 yr	1.6
Hospital records	Review of admissions	1–17 yr	1–2
Physicians' surveys	Analysis of questionnaires	6 mo	10
Prescribing surveys	Analysis of questionnaires	1 yr	10
Community surveys	Examination by physicians	2 yr	13

Data from Klainer et al.[2]

TABLE II Estimated Prevalence and Frequency of CHF in the U.S. Age 45 and over for 1960, 1970 and 1980

	Prevalence (000)	Incidence (000)
1968*	1,400	220
1970*	1,700	250
1980*	1,900	300
1983†	2,300	400

* Projection from Gibson et al.[3]
† Framingham rates applied to 1981 census.
Data from Gibson et al.[3]

TABLE III Average Annual Incidence of Cardiac Failure: 20-Year Follow-Up*

Age (yr)	Rate per 1,000 Men	Rate per 1,000 Women
45–54	1.8	0.8
55–64	4.3	2.7
65–74	8.2	6.8
Total	3.7	2.5

* Data from Kannel et al.[6]

TABLE IV Survival in Congestive Heart Failure in Men and Women Aged 55 to 74

Years after Diagnosis	Percent Surviving CHF* Men Total	Men Without CHD	Women Total	Women Without CHD
2	69.0	71.0	79.1	74.1
4	48.5	52.3	65.9	65.8
6	36.9	33.3	46.1	50.6
8	22.7	20.0	35.9	36.2

* Survivors of first acute episode only.
Data from Kannel et al.[6]

Survey studies of physicians in two U.S. counties Montgomery, North Carolina, and Caledonia, Vermont) were conducted in 1962 by Gibson et al[3] and provided prevalence rates for all ages and both sexes of to 10/1,000 population. Age-specific rates demonstrated a remarkable increase in CHF with increasing ge. The incidence of new cases during the survey period projects to 3.8/1,000 per year in one county and 5.0/1,000 population per year in the other.

Based upon these data, Gibson et al estimated that in 1960 1.4 million persons in the US had CHF and that 1.7 million would have it in 1970 and to 1.9 million in 1980. Similarly, the estimated incidence of new cases was projected to rise from 220,000 to 250,000 to 300,000 (Table II). The projection for 1980 based on the physician survey in the 2 rural counties in the early 1960s is not substantially different from that based on the Framingham rates and the 1981 U.S. census.

Incidence

Aside from the aforementioned physician survey information, incidence data on the occurrence of CHF in the general population were almost nonexistent before the Framingham study. Using uniform criteria for diagnosis based on a schema that had worked well for a rheumatic fever study, data were compiled for 20 years of follow-up of 5,192 men and women who had no evidence of cardiac failure on entry.[4,5] Of these, 117 men and 102 women aged 45 to 74 years developed definite CHF. Age-specific rates doubled for both men and women at each decade, averaging 3.7/1,000 for men and 2.5/1,000 for women (Table III). The rate of cardiac failure in men exceeded that for women at all ages, presumably because of the greater prevalence of coronary heart disease in men.

Prognosis

The natural history of cardiac failure in the absence of treatment intended to improve myocardiac contractility or reduce edema or afterload is not available. Neither are controlled trial data to assess the impact of these treatment modalities on long-term mortality, although the clinical impression that short-term mortaility improves is probably accurate. The Framingham study found that the probability of death within 4 years of first diagnosis of cardiac failure was 52% for men and 34% for women, regardless of the underlying cause. (Table IV).[6] Within 5 years of a first myocardial infarction, 14% of men had CHF, and half were dead within 5 years.[4,5]

From a population of 1,964 medically treated patients found to have significant coronary artery disease during cardiac catheterization at Duke University Medical Center over a 12-year period, the prognosis of 236 patients with a history of cardiac failure was examined.[7]

The ejection fraction had been determined in 196 (83%) of these patients.

Of 133 deaths, 54 (41%) occurred within 2 hours of the onset of symptoms and were classified as sudden. Forty deaths (30%) were the result of progressive cardiac failure. Other fatal cardiac events were due to recurrent myocardial infarctions (n = 28) and stroke (n = 6). There were 18 nonfatal infarctions and 6 noncardiovascular deaths. The cumulative initial event rates were 37% and 67% at 1 and 5 years, respectively (Fig. 1). The survival probabilities were not different for New York Heart Association classes I to III, 75% and 48% at 1 and 5 years, but were notably worse for class IV, 34% and 18% at 1 and 3 years, respectively (Fig. 2).

The prognosis of 77 patients with functional class III or IV heart failure was evaluated prospectively at the University of Pennsylvania over 5 to 40 months (average 12).[8] Survival was computed by life-table analysis and related to clinical hemodynamic M-mode echocardiography and 24-hour Holter monitoring data. Overall survival was 52% at 1 year and 32% at 2 years. The cause of cardiac mortality was equally divided between sudden death and cardiac failure. The survival rate for patients with underlying coronary artery disease was no different from other causes.

Survival experience was described[9] in men with severe cardiac failure caused by coronary artery disease or idiopathic dilated cardiomyopathy. This population consisted of patients with persistent symptoms despite therapy, who were referred for management and long-term follow-up by cardiologists at the Veterans Administration Hospitals in Philadelphia and Minneapolis. A total of 182 patients, 95 with cardiomyopathy secondary to coronary artery disease and 87 with idiopathic dilated cardiomyopathy, were followed for an average of 12 months. During the follow-up period, 88 deaths occurred, 58 in the coronary artery disease group and 30 in the idiopathic group, a difference significantly greater than expected by chance ($p < 0.01$). Forty-two percent of the deaths in the coronary artery disease group and 50% of those in the idiopathic group were classified as sudden. Among the patients who underwent coronary arteriography, mortality in the coronary artery disease group was 49% at 1 year and 82% at 2 years, compared with 17% and 48% at 1 and 2 years, respectively, for patients with idiopathic dilated cardiomyopathy. Survival rates for the etiologic groups were analyzed separately and together. By 3 years only 24% of the patients were alive, but the cumulative mortality was clearly higher for the coronary artery disease group at 12 and 24 months (Fig. 3).

Thus, CHF is highly lethal even from the time of first diagnosis, and can only be described as grim once symptoms do not yield to treatment.

Risk Factors

Overt heart disease whether ischemic, rheumatic or congenital, plus advancing age, are the principal determinants of the incidence of CHF. There are other, more subtle predictors, some of which are etiologic and some merely markers of deteriorating myocardial function. Among the former, none is more dominant

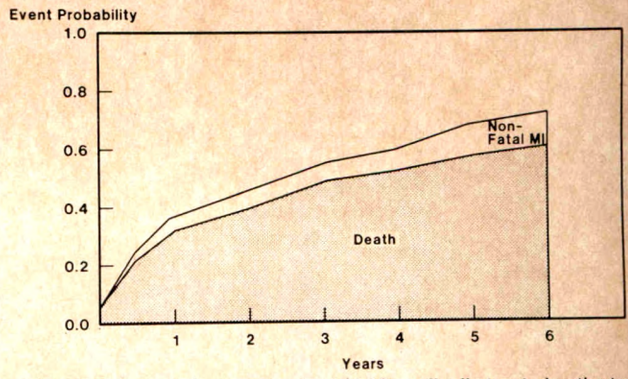


FIGURE 1. Cumulative event rates in 236 medically treated patients with coronary disease and congestive heart failure. MI = myocardial infarction.

than hypertension. And, although this association was noted much earlier, it was the report of 16 years of follow up of the Framingham study that placed this in its present perspective.[4–6]

Systemic hypertension: Definite hypertension preceeded CHF in 75% of cases, and was the rule even in those patients who also had coronary artery disease and rheumatic heart disease. Indeed, coronary artery disease not accompanied by hypertension was a precursor to cardiac failure in only 10% (Fig. 4). Women were as susceptible as men to elevated blood pressure as a precursor to CHF. In regression models of CHF incidence on blood pressure, the contribution of blood pressure was also independent of other cardiovascular risk factors. This prediction of risk applies to diastolic, mean and systolic pressure equally well. Indeed, the coefficients for the regression of CHF incidence on systolic pressure were larger than those for diastolic (0.643 vs 0.466).

Diabetes mellitus: Other frequently noted concomitant chronic diseases, such as diabetes mellitus, chronic lung disease, stroke and claudication, are all probably related to advanced age, but only diabetes

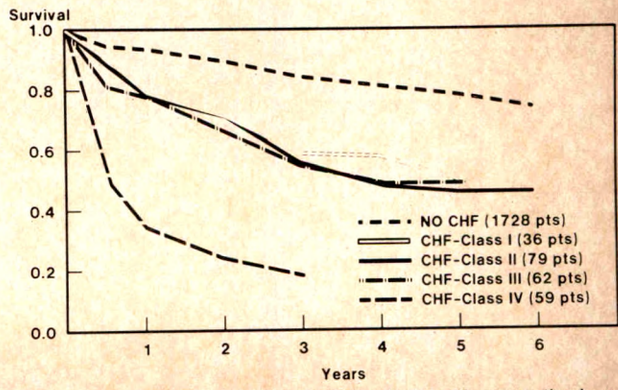


FIGURE 2. Survival probabilities in 236 patients with congestive heart failure (CHF) and coronary disease according to New York Heart Association CHF classes compared with 1,728 patients with no history of CHF.

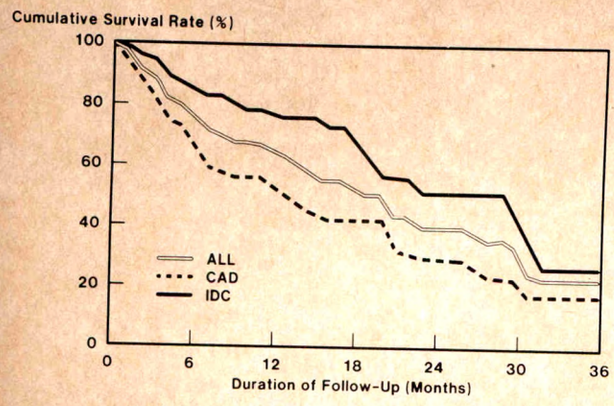


FIGURE 3. Survival rates in patients with severe chronic left ventricular failure caused by cardiomyopathy. CAD = coronary artery disease; IDC = idiopathic dilated cardiomyopathy.

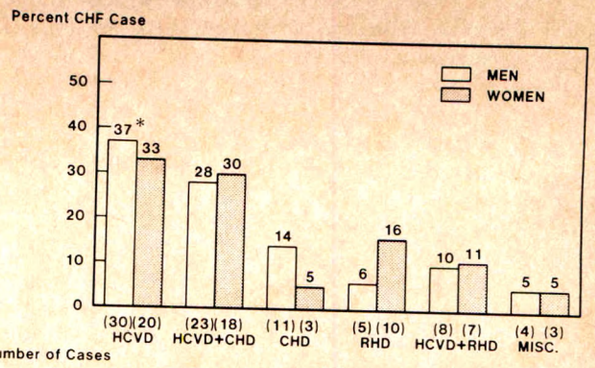


FIGURE 4. Etiology of congestive heart failure (CHF) (16-year follow-up results) for men and women 30–60 years of age at entry into the Framingham study. CHD = coronary heart disease; HCVD = hypertensive cardiovascular disease; RHD = rheumatic heart disease; Misc = miscellaneous.

mellitus may be uniquely related to CHF. The Framingham study examined this relation in some detail, noting antecedent diabetes in 16% of patients who had cardiac failure.[10] This apparent excess reflected a greater impact on women than men (Table V). Diabetic women had a 5-fold increase in incidence of CHF while diabetic men only had a 2-fold greater risk compared with nondiabetic persons. This excess risk of CHF conveyed by the diagnosis of diabetes applied to all ages, but was substantially limited to those diabetics treated with insulin, who constituted 40% of those diagnosed (Table VI). More than half of the patients with diabetes who had cardiac failure were taking insulin. This finding may implicate insulin-dependent, ketotic, insulinopenic diabetes of early onset as the promoter of cardiac failure rather than mere duration or severity of the diabetes. A sizable and unique effect of diabetes persisted in multivariate analysis, which also took into account other coronary heart disease risk factors and other possible contributors to CHF incidence. Thus, rather than simple acceleration of coronary atherosclerosis, it has been suggested that it is microangiopathy similar to that seen in the skin, retina and kidney, and known to be more severe in the insulin-dependent diabetics, that increases the risk of CHF.

Other factors: Proteinuria, obesity and cigarette smoking were also examined in the Framingham cohort as possible promoters of CHF.[6] Proteinuria was associated with an excess risk of cardiac failure, even when other cardiovascular risk factors associated with proteinuria were taken into account. A modest effect of weight on age-adjusted risk of CHF for all ages combined was noted. Cigarette smoking was, at best, a weak predictor of cardiac failure in men, but doubled the risk in women.

Prognostic Factors

The studies at Duke University Medical Center found no distinction among New York Heart Association classes I to III patients in terms of a number of baseline characteristics (abnormalities), including a history of myocardial infarction.[7] On the other hand, class IV patients had substantially more abnormalities (Fig. 2). Moreover, multivariate analysis demonstrated that the most important predictors of survival were class IV CHF together with significant left main stenosis, decreased ejection fraction and widened a-v oxygen difference. Unfortunately, the considerable overlap of hemodynamic measurements between survivors and nonsurvivors, especially in classes I to III, limited the

TABLE V Risk of Congestive Heart Failure According to Sex and Diabetic Status at Each Biennial Examination: 18-Year Follow-Up Study

Diabetic Status	Person-Years at Risk	Incidence: Crude Annual Per 10,000	Incidence: Age Adjusted Per 10,000*	Relative Risk
Men Aged 45 to 74 Years				
Nondiabetic	26,988	31.87	32.14	
Diabetic	1,226	89.72	75.98	2.36†
Women Aged 45 to 74 Years				
Nondiabetic	35,322	19.53	19.75	
Diabetic	1,190	142.85	101.60	5.14†

* Indirect method.
† Significant at $p < 0.05$ ($\chi^2 = 6.50$).
‡ Significant at $p < 0.01$ ($\chi^2 = 12.53$).

usefulness of these variables as discriminators among individual patients and in evaluation of therapeutic interventions. Moreover, these hemodynamic variables often do not correlate well with the symptomatic status of patients with CHF.

The University of Pennsylvania study found a correlation between survival and global circulatory dysfunction as indicated by functional class during the first 4 months of enrollment, but thereafter found no clinical or hemodynamic variable that correlated with survival.[7] The study also found a positive correlation of ventricular tachycardia (5 or more consecutive ventricular premature depolarizations) with functional class and nonsudden cardiac mortality, but no variable that correlated with sudden death (Fig. 5).

On the other hand, the Veterans Administration study of patients with refractory symptoms (classes III and IV) found that the hemodynamic measures of left ventricular dysfunction correlated well with prognosis. In addition, it noted a worse prognosis in patients with higher systemic vascular resistance, lower left ventricular stroke work and high levels of circulating catecholamines (Figures 6 and 7).[9] The need to activate the adrenergic system and perhaps the renin-angiotensin-aldosterone system appears to herald a particularly grave prognosis. In view of the correlation of hemodynamic variables with prognosis even in advanced cases, the Veterans Administration investigators believed their use may have value if their modification would alter prognosis. The question is: which of the variables to intervene on, or because the options include cardiotonics, diuretics and afterload reducers, in what combination and sequence should one commence?

Implications

Based on the criteria used in the Framingham study and the observed rates, the estimate for the 1983 inci-

TABLE VI Regression of the Incidence of Congestive Heart Failure (Without Prior Coronary or Rheumatic Heart Disease*) on Treatment of Diabetes: 18-Year Follow-Up Study

Treatment	Bivariate Coefficient†	t Value‡
Men Aged 45 to 74 Years		
Insulin	1.76	3.26
Oral hypoglycemic agent	0.63	0.66
Other	0.92	0.90
Women Aged 45 to 74 Years		
Insulin	2.21	4.47
Oral hypoglycemic agent	0.56	0.54
Other	1.49	1.45

* To be included in this group at a given examination (n), the patient must not have had coronary or rheumatic heart disease on or before examination (n + 1).

† The covariate function was estimated by the method of Walker and Duncan using the variables type of diabetic treatment and age.

‡ A value of 1.96 is significant at the 0.05 level.

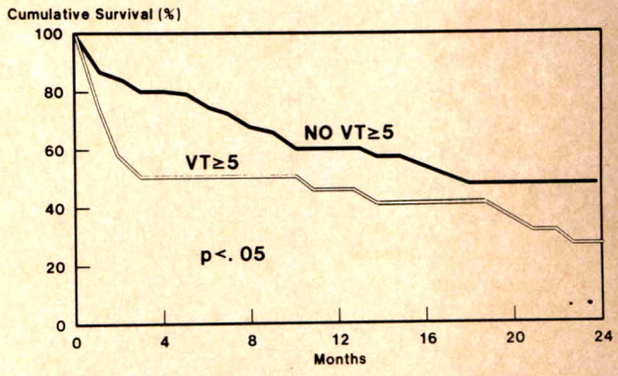


FIGURE 5. Comparison of cumulative survival rates for patients with and without 5 or more consecutive ventricular premature depolarizations (>5 VT) in the University of Pennsylvania study. VT = ventricular premature depolarizations.

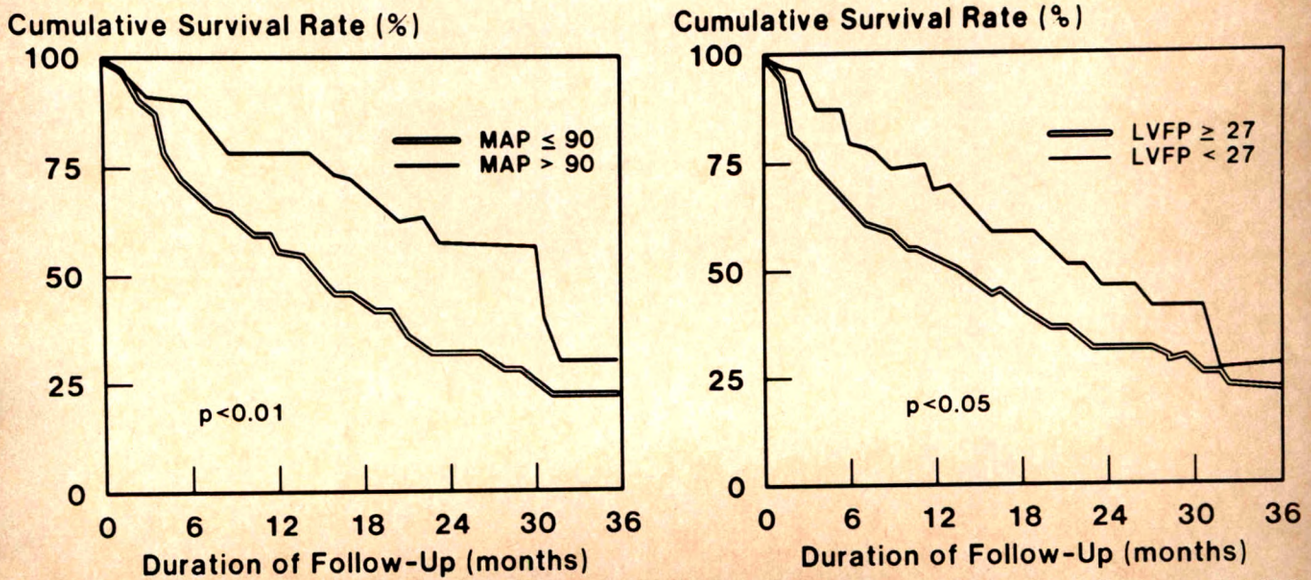


FIGURE 6. Survival rates in patients with severe chronic left ventricular failure caused by cardiomyopathy according to blood pressure and left ventricular filling pressure (LVFP) at entry. MAP = mean arterial pressure. Reproduced from Franciosa et al[9] with permission of the publisher.

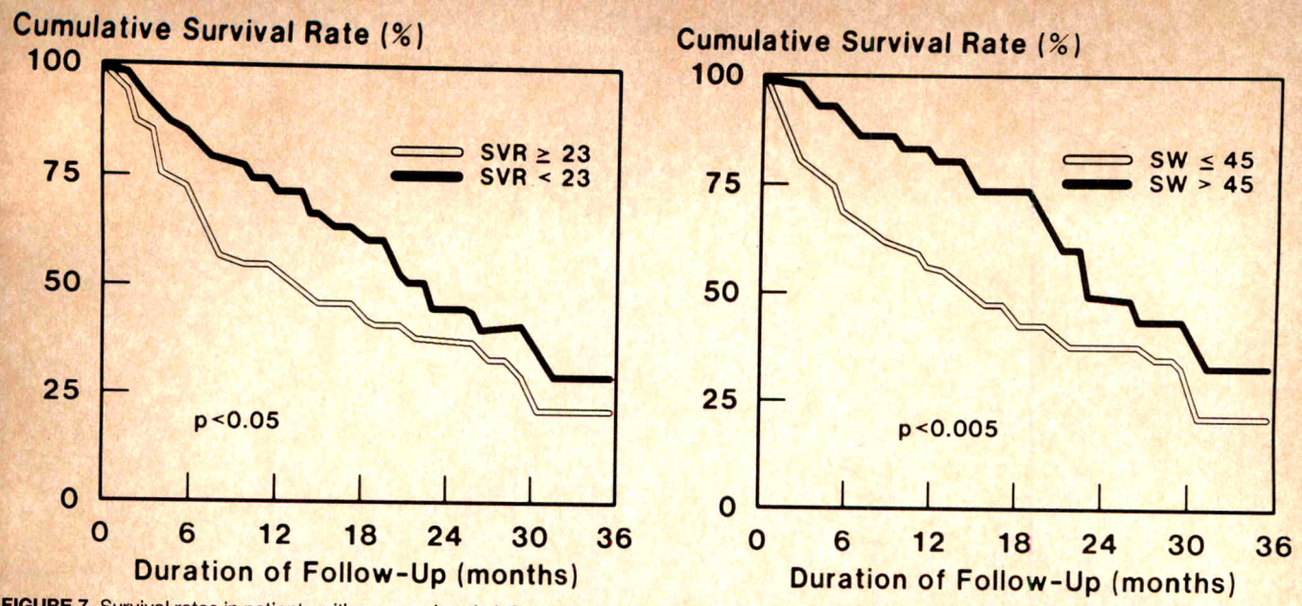


FIGURE 7. Survival rates in patients with severe chronic left ventricular failure caused by cardiomyopathy according to systemic vascular resistance and left ventricular stroke work at entry. SVR = systemic vascular resistance (units): SW = stroke work. Reproduced from Franciosa et al[9] with permission of the publisher.

dence of CHF in the United States is 214,000 men and 184,000 women.

The estimate of prevalence based on the 2-county study of Gibson and applied to the 1981 census figures is 2,300,000. In 1981, 1.8 million physicians' office visits were for CHF. Over 1.5 million hospital discharges in 1982 bore the diagnosis of CHF, with the rate of hospitalization for CHF ranging up to 20/1,000 population (2%) in the older age category. CHF was the underlying or contributing cause of death in 164,000 persons in 1978. All of these figures are strikingly related to age, with men having higher rates than women at all ages. Nearly 90% of these patients have hypertension or coronary heart disease or both, with hypertension predominating as the antecedent underlying condition.

The prognosis after first diagnosis is grim; less than half survive after 5 years. Prognosis is related to the degree of myocardial dysfunction. For example, functional class IV has a 1-year survival rate of less than 50%, with nearly half of the deaths classified as sudden.

If there exists a wide spectrum of degree of myocardial dysfunction, ranging from that which can only be detected by sophistocated measures (invasive and noninvasive) during stress (class 0), through that which can be recognized clinically under varying degrees of stress (classes I and II), to global insufficiency even at rest (class IV), then the challenge is to develop more effective drugs for both the management of overt cardiac failure and the prevention of its progression.

Ultimately, the goal must be prevention. Given the dominance of hypertension as a risk factor in the development and progression of CHF, drugs that are effective in controlling blood pressure through afterload reduction also have the potential for impacting on the natural history of CHF.

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Pathophysiology of Congestive Heart Failure

WILLIAM W. PARMLEY, MD

Over the past several years, additional information has been accumulated on the pathophysiology of congestive heart failure. The primary cardiac defect is a decrease in intrinsic contractility of the myocardium, usually brought on by prolonged pressure or volume overload. Several associated biochemical changes have been described, although no precise cause-and-effect relation has been determined. A number of neurohumoral changes occur, which increase systemic vascular resistance. This increased resistance contributes further to a decrease in cardiac output. In fact, many such "compensatory mechanisms" that are initially beneficial may overshoot and produce deleterious hemodynamic effects. Therapeutic interventions such as diuretics, inotropic drugs and vasodilators are frequently helpful by correcting compensatory mechanisms that overshoot. (Am J Cardiol 1985;55:9A–14A)

Congestive heart failure (CHF) is a common clinical syndrome but its pathophysiologic factors may vary considerably among patients. An overview of the major factors involved in CHF and a discussion of the therapeutic implications of these changes are presented.

Causes of Heart Failure

Table I lists some of the major pathophysiologic processes that contribute to the development of CHF. Pressure overload is commonly caused by systemic hypertension or by outflow tract obstruction, such as valvular aortic stenosis. Similarly, the right ventricle can be affected by pulmonary hypertension of any origin. Volume overload can be caused by several different conditions, such as aortic or mitral regurgitation. High output states, which will be discussed later, can also contribute to volume overload of the left ventricle. Selective volume overload of each ventricle can be caused by certain forms of congenital heart disease. For example, a patient with an atrial septal defect and a large left-to-right shunt will have volume overload of the right ventricle, whereas the left ventricle will be unaffected. Prolonged pressure or volume overload leads to intrinsic changes in myocardial contractility, which appear to be mostly irreversible.[1] This decline in contractility eventually results in the common clinical syndrome of CHF.

Loss of muscle as a cause of CHF is best exemplified by the patient with coronary artery disease who has one or more myocardial infarctions. This loss of muscle decreases the pumping capabilities of the heart and can lead to the same irreversible changes in the remaining normal myocardium. In acute myocardial infarction, for example, loss of 40% or more of the myocardium results in cardiogenic shock.[2]

A decrease in the intrinsic contractility of heart muscle is exemplified by conditions such as volume and pressure overload and cardiomyopathy. The last general factor listed in Table I is restricted filling of the heart. This is exemplified by constrictive pericarditis, pericardial tamponade or conditions in which a stiff ventricular chamber restricts filling. Examples of the latter include endomyocardial fibrosis or a thick hypertrophied ventricle with decreased compliance. In many of these settings, the atrial contribution to ventricular filling becomes an important mechanism for maintaining filling of the left ventricle. For example, when atrial fibrillation develops in patients with hypertrophic cardiomyopathy, the loss of the A-wave contribution frequently leads to abrupt development of the signs and symptoms of CHF.

With these general factors in mind, Table II is a list of the common clinical causes of heart failure seen in patients with this syndrome. In our experience, coronary artery disease is the most common cause of CHF. It comprises approximately two-thirds of our patients with severe class IV heart failure. It appears that systemic hypertension is becoming a less common cause of severe CHF, presumably reflecting better recognition and control of elevated blood pressure. Similarly, rheumatic valvular disease appears to be declining as a common cause of severe CHF. This probably reflects the decreased incidence of the condition and better surgical management at an earlier stage of the disease. Calcific aortic stenosis in older patients, however, remains an

From the Department of Medicine, University of California and the Cardiovascular Division, H. C. Moffitt Hospital, San Francisco, California.

Address for reprints: William W. Parmley, MD, Room 1186, Moffitt Hospital, University of California, 505 Parnassus Avenue, San Francisco, California 94143.

TABLE I Pathophysiology of Congestive Heart Failure—General Features

Pressure overload
Volume overload
Loss of muscle
Decreased contractility
Restricted filling

TABLE II Common Causes of Congestive Heart Failure

Coronary artery disease
Systemic hypertension
Valvular heart disease
Cardiomyopathy
Congenital heart disease

TABLE III High Output Failure

Hyperthyroidism
Anemia
Paget's disease
Polyostotic fibrous dysplasia (Albright's disease)
Hypernephroma with bone metastases
Arteriovenous fistula
Dermatologic disorders
Acute glomerulonephritis
Hepatic cirrhosis

TABLE IV Pathophysiology of Congestive Heart Failure in Coronary Artery Disease

Loss of muscle
Ischemia
Aneurysm—paradoxical expansion, increased wall stress
Increased wall stress of remaining normal muscle
Decreased ventricular compliance

important cause, but it may be difficult to recognize because its manifestations are often relatively subtle. Cardiomyopathy is a not infrequent cause of CHF. Controversy has arisen as to whether these patients should undergo cardiac biopsy to determine the potential for immunosuppressive therapy.[3] Frequently, the cause of cardiomyopathy cannot be determined, although we presume that many idiopathic cardiomyopathies represent postviral events.

The most common cause of right-sided cardiac failure is left-sided cardiac failure. However, a number of important conditions lead to pulmonary hypertension and right-sided cardiac failure in the absence of direct involvement of the left ventricle. Mitral stenosis is one of these conditions, although its incidence appears to be decreasing in the U.S. Emphysema and chronic obstructive lung disease, particularly in association with smoking, are frequent causes of elevated pulmonary pressures and right-sided cardiac failure. Repeated pulmonary emboli may also cause this syndrome. Idiopathic pulmonary hypertension is not uncommon, yet there is inadequate knowledge regarding causative factors. Heart failure associated with congenital heart disease can occur at all ages, depending on the particular syndrome involved. Many cardiovascular abnormalities lead to CHF during the neonatal period and some are virtually incompatible with life. Earlier and more complete correction of many abnormalities has decreased the number of patients who present with CHF in their later years.

Cardiac Function in Heart Failure

By implication, most of the entities discussed so far lead to a reduction in cardiac output, which is one of the principal manifestations of the CHF state. However, high-output failure can be produced by a number of conditions. Furthermore, in some patients with reduced ventricular reserve any increased need for cardiac output can precipitate CHF. Table III lists some of the common causes of increased cardiac output that may contribute to CHF in either a primary or secondary fashion. Hyperthyroidism increases the need for cardiac output by increasing total body metabolism, as mediated by elevated levels of thyroid hormone. Anemia increases the need for cardiac output by reducing the oxygen-carrying capacity of a given quantity of blood. Many of the other conditions listed in Table III reflect disorders with arteriovenous fistulas, which shunt blood to the venous system without passing through the capillaries. Some dermatologic disorders, such as severe psoriasis, lead to a dramatic increase in skin blood flow, which is responsible for the increased need for cardiac output. In general, primary high-output failure is apparently uncommon. These and other causes of elevated cardiac output, however, should be considered as contributing or precipitating causes in patients whose ventricular reserve is reduced for other reasons.

Because coronary artery disease is the major cause of severe CHF in the U.S., it is worthwhile to comment further on the pathophysiologic mechanisms involved in producing CHF in this setting. Table IV lists the major factors that contribute to CHF in the presence of coronary artery disease. The first and most important is the loss of muscle because of myocardial infarction and subsequent scar formation. Reduction in the pumping ability of the heart and ventricular reserve naturally follow from reduction in the number of contractile elements. Ischemia is also an important way of reducing function. As angina or acute ischemia develops, there is an abrupt reduction in regional function, since ischemic muscle rapidly loses its ability to contract.[4] In patients with unstable angina, or occasionally with more chronic angina, restoration of blood supply by coronary bypass grafting results in improved regional wall motion, suggesting that more chronic ischemia can contribute to a reduction in ventricular function.[5]

Aneurysms can contribute to ventricular dysfunction in a number of ways. During the acute process of ischemia and infarction, ischemic muscle not only loses its ability to contract, but it invariably bulges paradoxically during systole. This paradoxical systolic expansion can reduce forward stroke volume as this portion of the ventricle accepts a volume of blood, depending on the size and compliance characteristics of the involved area. As the affected muscle passes through the necrotic to the healing stage, development of a fibrous scar reduces the compliance characteristics

of the aneurysm, so there is no longer the same degree of paradoxical systolic expansion. In vitro studies of aneurysmal tissue have pointed out the stiff character of ventricular aneurysms and the inability of fibrous tissue to stretch during systole.[6] The apparent paradoxical expansion occasionally seen on ventriculograms may represent stretching of surrounding muscle, which may be ischemic. Aneurysms also increase ventricular size, which may be adverse in increasing wall stress in the remaining normal muscle by the LaPlace relation.

Thus, reduction of ventricular size by aneurysmectomy may be an important means of reversing this detrimental effect of an aneurysm. When muscle is lost during an infarction, there is increased loading of the remaining normal muscle. In the same way that pressure or volume overload can eventually lead to an irreversible reduction in intrinsic contractility, it is likely that the same stresses may be operative in the normal muscle of patients with large myocardial infarcts.

One aspect of considerable interest in the patient with coronary artery disease is the decrease in ventricular compliance that appears to accompany the process of scar formation after infarction. Further, during acute angina pectoris, it appears that the ventricle becomes stiffer, presumably owing to some degree of ischemic contracture or relaxation abnormalities.[7] This tends to reduce ventricular filling and requires elevated filling pressures. For example, some patients with coronary disease have restriction of filling, rather than reduction in systolic function, as the primary mechanism for their pulmonary congestion.[8] Detrimental effects on both systolic and diastolic function, therefore, are caused by coronary disease and contribute to the heart failure syndrome.

Precipitating Events in Heart Failure

In trying to evaluate the cause of CHF in a patient, it is important to evaluate not only the underlying cause, but also the precipitating causes. The difference between worsening of the intrinsic CHF and superimposition of a precipitating cause is important in guiding therapy and determining prognosis. Many of the common precipitating causes are listed in Table V.

Reduction of therapy is one of the most common and important precipitating causes of CHF. Salt and dietary excesses are frequent causes for accumulation of extra fluid and worsening of CHF. Similarly, reduction or discontinuation of pharmacologic therapy, owing to poor compliance, running out of medications, etc, is a common cause that must be considered.

Arrhythmias can often aggravate, and in some circumstances precipitate, severe CHF. For example, the development of rapid supraventricular or ventricular tachycardia can worsen CHF dramatically in patients with reduced ventricular reserve. Viral or bacterial infections or superimposed pulmonary embolism are frequently responsible for worsening of the CHF state. Superimposition of physical, environmental or emotional stress also adversely affects the heart, presumably by increasing the demands on the heart in the setting of reduced ventricular reserve. Bacterial endocarditis, myocarditis and inflammation are obvious causes of worsening CHF. We have already discussed some forms of high-output CHF, which are more commonly manifested as precipitating causes of CHF. Finally, the development of unrelated illnesses or a second form of heart disease can also provoke worsening heart failure. For example, in the patient with valvular heart disease, the development of coronary artery disease can precipitate CHF and other cardiac events, because of the superimposed ischemia.

TABLE V Precipitating Causes of Congestive Heart Failure

Reduction of therapy
Arrhythmias
Systemic infection
Pulmonary embolism
Physical, environmental and emotional stress
Cardiac infection and inflammation
High output states
Unrelated Illness
Second form of heart disease

TABLE VI Myocardium in Congestive Heart Failure

1. Mechanical alterations
Decreased velocity of shortening
Decreased force development
Decreased maximum rate of force development
Little or no change in passive length-tension relations
No change in series elastic
2. Biochemical alterations
Decreased actomyosin ATPase activity
Increased collagen
Decreased myocardial norepinephrine
Decreased synthesis of norepinephrine
Decreased function of sarcoplasmic reticulum
? Decreased high-energy phosphates
? Excess myoplasmic calcium

Myocardial Contractility in Heart Failure

Let us now turn to some of the changes associated with a reduction in intrinsic contractility of the myocardium in CHF. In many circumstances, it is the intrinsic reduction in contractility that contributes primarily to the heart failure state, and that appears to be essentially irreversible. Table VI lists some of the mechanical and biochemical changes that have been noted. In vitro studies of the mechanics of myocardial contraction in animal models of heart failure have noted a variety of changes.[9] First, there is a decreased ability of failing muscle to develop force and to shorten with a given velocity at specified loading conditions. The decrease in velocity of shortening is conceptually related to the observed decrease in maximal rate of force development.

The elastic properties of failing heart muscle have also been examined in animal models of CHF. In general, there is little or no change in the passive length-tension relations of isolated failing heart muscle. Yet this does not obviate the fact that there can be dramatic changes in passive pressure-volume relations of the intact ventricle. Hypertrophy of the ventricle per se can

TABLE VII Hormonal Changes in Congestive Heart Failure

Increased circulating catecholamines
Increased renin-angiotensin-aldosterone
Increased arginine vasopressin

TABLE VIII Compensatory Mechanisms in Congestive Heart Failure That Can Overshoot

Excessive rise in preload
Excessive increase in systemic vascular resistance
Excessive increase in heart rate
Excessive increase in catecholamines
Excessive activation of renin-angiotensin-aldosterone system

produce dramatic changes in compliance, even though each unit of muscle may have relatively normal passive length-tension relations.[10] Another elastic property of muscle is the series elastic, which can be measured by quick release techniques during contraction. There does not appear to be any change in the series elastic properties of failing heart muscle,[11] which may reside primarily in the crossbridges.

Several biochemical alterations have been described during CHF, although it has been very difficult to determine any cause-and-effect relation between a given biochemical change and the heart failure state. That is, one cannot point to any single biochemical alteration as a cause for the reduction in intrinsic contractility. One of the more interesting changes is the decrease in actomyosin-ATPase activity.[12] At the crossbridge, actin-activated myosin has ATPase activity, which releases energy for contraction. Previous studies suggest that actomyosin-ATPase activity is related to velocity of shortening, an interesting correlation between muscle mechanics and biochemistry.[13] In CHF, there is a decrease in both velocity of shortening and actomyosin-ATPase activity. This is mediated by an alteration in myosin isozymes, with a shift from fast to slow isozymes. Thus, this shift in enzymatic activity is not only associated with a decrease in velocity of shortening, but also with a decrease in energy expenditure.[14] The decrease in oxygen consumption, therefore, may be of benefit to the heart if there is a limitation of oxygen supply, either because of hypertrophy or coronary artery disease.

During the process of hypertrophy and heart failure, increased myocardial collagen content has been observed.[15] This may be part of the hypertrophy process itself. Decreased stores of norepinephrine have been noted in some animal models of CHF.[16] This presumably reflects an increase in sympathetic tone and release of catecholamines in an attempt to maintain cardiovascular conpensation in the face of a decrease in contractility. In some studies, a decrease in synthesis of norepinephrine was also noted, because of a depression of the enzyme, tyrosine hydroxylase.[17] Decreased function of the sarcoplasmic reticulum has also been noted with a decreased rate of uptake of calcium and decreased stores of calcium.[18]

Initial studies of high-energy phosphates in CHF suggested that there was no reduction and concluded that depletion of high-energy phosphates could not adequately explain the CHF state.[19] More recent studies suggest that in some instances, there can be depletion of high-energy phosphates during CHF.[20] The cause-and-effect relation between these 2 factors, however, is not established. In some instances of CHF, such as that produced by ischemia or in the hereditary congestive cardiomyopathy of the Syrian hamster, excess calcium accumulation has been demonstrated as part of the CHF process.[21] Because excess calcium can produce a number of deleterious effects in the myocardium, including depression of mitochrondrial function, the pathophysiologic role of excess calcium deserves further study.

Peripheral Factors in Heart Failure

A number of hormonal changes occur in CHF, some of which are listed in Table VII. There are increased circulating catecholamine levels owing to an increase in sympathetic tone and release of catecholamines from the adrenal medulla. There is a general relation between the severity of CHF and the level of circulating catecholamines,[22] which presumably are designed to maintain cardiovascular function in the face of decreased intrinsic contractility. The renin-angiotensin-aldosterone system is also frequently activated. Angiotensin II has several potentially adverse effects in CHF. First, it is a potent vasoconstrictor, and thus may directly contribute to an excessive increase in systemic vascular resistance. Second, it facilitates sympathetic outflow, and therefore enhances levels of circulating catecholamines. Third, it leads to an increased release of aldosterone, which promotes further retention of salt and water. Certainly, the activation of the renin-angiotensin-aldosterone system sets the stage for the use of angiotensin converting enzyme inhibitors in CHF.[23]

Another vasoconstrictive hormone that is elevated in CHF is arginine vasopressin.[24] It is unclear how much this enzyme contributes to the elevated systemic vascular resistance seen in CHF, and further studies are needed to put the role of this hormone into better perspective.

One of the more interesting concepts developed over the past few years is that although compensatory mechanisms may be helpful in maintaining cardiac function, these mechanisms have the potential for overshooting and producing deleterious effects. Some of these compensatory mechanisms are listed in Table VIII. The retention of salt and water that occurs because of decreased cardiac output and renal perfusion can lead to an excessive increase in preload. Initially, an increase in preload is effective in increasing cardiac output through the Frank-Starling mechanism. As preload increases further, however, it leads to congestive symptoms without any further improvement in cardiovascular performance.

Evidence is convincing that systemic vascular resistance is often too high in the CHF state. This is part of the vicious cycle of heart failure. As cardiac output decreases, systemic vascular resistance increases through the potent neurohumoral reflex mechanisms that have been described. This increased resistance, however, can

further increase the resistance to ejection of blood, reduce cardiac output and therefore lead to a steady-state condition in which cardiac output is lower and systemic vascular resistance is higher than optimal for the patient. The best evidence to support this phenomenon is pharmacologic; i.e., potent arteriolar drugs can improve forward cardiac output in CHF without other major effects on hemodynamics.[25]

Heart rate is almost invariably increased in the CHF state, presumably reflecting an increase in circulating catecholamines and sympathetic tone. The increase in heart rate is certainly important in maintaining cardiac output in the face of a fixed, low stroke volume. Under certain circumstances, however, an excessive heart rate may be deleterious. For example, heart rate is directly linked to myocardial oxygen consumption, so that the higher the heart rate, the greater the need for coronary blood flow. Additionally, with increased heart rate, the diastolic time during which coronary flow occurs is shortened. Therefore, an increase in heart rate can not only increase demand, but can also potentially reduce supply, and thus adversely affect the patient with coronary artery disease. There may be adverse effects in patients with severe hypertrophy or cardiomyopathy.

In experimental animals, myocardial necrosis can be produced by massive infusions of catecholamines, such as isoproterenol.[26] It is unlikely that direct myocardial necrosis is produced in patients by an excess of catecholamines, although catecholamines can adversely affect patients in a number of ways. They produce an excessive rise in systemic vascular resistance, which can reduce cardiac output. Furthermore, they stimulate both heart rate and contractility and, therefore, contribute to an increase in myocardial oxygen consumption. If this occurs in the setting of reduced coronary reserve, the propensity for ischemia is considerable.

Although excessive activation of the renin-angiotensin-aldosterone system was already discussed, it is important to note that the initial effects of activation of this system may be beneficial, but can become deleterious in severe heart failure.

Therapeutic Approach to Heart Failure

By understanding the pathophysiologic mechanisms occurring in CHF, therapeutic solutions can be designed to each problem. This general approach is illustrated in Table IX, and will be briefly discussed. The increased preload or filling pressures of the right and left ventricles are responsible for the symptoms of pulmonary and peripheral congestion. A therapeutic goal is to reduce salt intake and use diuretics. In addition, venodilators are effective in reducing right- and left-atrial filling pressures by dilating peripheral veins and redistributing blood volume, with more in the periphery and less in the chest.[25]

The low cardiac output and accompanying high systemic vascular resistance seen in CHF are primarily responsible for the symptoms of fatigue, presumably caused by poor perfusion of skeletal muscle. Arteriolar dilators are effective in reducing systemic resistance and increasing forward cardiac output. This combination—decreasing an elevated preload and increasing a low cardiac output—represents the most important therapeutic hemodynamic goal in patients with CHF.[25]

TABLE IX Therapeutic Principles in Congestive Heart Failure

Problem	Therapy
Increased preload	Salt restriction, diuretics, venodilators
Low cardiac output, high systemic resistance	Arteriolar dilators
Decreased contractility	Positive inotropic agents
Rapid heart rate, atrial fibrillation, sinus tachycardia	Increase atrioventricular block, improve left ventricular performance (? β blockade)

The decrease in intrinsic contractility seen in the CHF state sets the stage for the use of positive inotropic agents. Digitalis is the most widely available oral agent, and appears to have modest beneficial effects on hemodynamics. A number of intravenous drugs are available, particularly in the catecholamine class, which can be effective in patients with severe, acute CHF. Some intravenous drugs, such as dobutamine, are reported to be effective when infused intermittently in patients with severe heart failure.[27] A variety of positive inotropic agents are being investigated, and most of them have peripheral vasodilating qualities. Certainly, the combination of peripheral vasodilation and increased contractility is an attractive one for a given agent in reversing some of the major pathophysiologic changes that occur in CHF.[28]

A rapid heart rate during CHF often signals the severity of the CHF state. There is speculation that the heart rate response may be too rapid in some patients, and may therefore become a compensatory mechanism that overshoots. Certainly in atrial fibrillation with a rapid ventricular response, this is the case. The therapeutic reduction of ventricular rate by atrioventricular block with drugs such as digitalis can be dramatically effective in helping such patients. This is particularly true for the patient with mitral stenosis, but is equally true for virtually all other patients. There is some debate as to whether or not a rapid sinus tachycardia, in and of itself, can be deleterious. Use of β-blocking drugs has been proposed for patients with congestive cardiomyopathy, particularly those who appear to have heart rates out of proportion to the severity of CHF.[29] Whether attempts to reduce heart rate directly with β blockade may be effective in certain groups of patients is not clear. One group that might benefit would be patients with severe coronary disease. These patients have excess catecholamine secretion with only moderate heart failure; thus, they can tolerate β-blocker therapy. In general, a rapid sinus tachycardia tends to abate as left ventricular performance improves by any of the interventions discussed. This presumably reflects a reduction in the sympathetic tone and circulating catecholamines that are affecting the SA node.

In summary, we have discussed the general changes occurring in the CHF state that determine the pathophysiology of this condition. Certainly, a better understanding of the pathophysiologic factors allows us

to approach the patient more rationally in terms of therapeutic regimens. It is clear that changes both in systolic and diastolic function can produce adverse effects on performance. It is also clear that appropriate correction of compensatory factors that may have overshot is a major goal of the current therapeutic approach to patients with severe CHF.

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Neurohumoral Mechanisms Involved in Congestive Heart Failure

GARY S. FRANCIS, MD

Congestive heart failure (CHF) promotes an array of biologic changes that are largely designed to compensate for reduced flow. These include activation of the sympathetic nervous system and the renin-angiotensin system, as well as the release of arginine vasopressin. The ultimate expression of these compensatory mechanisms is heightened vascular tone, increased sodium and water retention and antidiuresis. The peripheral circulation is normally under the fine control of circulating and neuronally released moieties, which can directly or indirectly alter vascular tone. Angiotensin II appears to be a key element in this regard because of its multiple biologic activities. Direct arteriolar vasoconstriction, facilitation of norepinephrine release and stimulation of aldosterone are some of the activities that are likely to be of major importance in the syndrome of CHF. Therefore, it is not surprising that converting enzyme inhibitors have a growing role as treatment. Other pharmacologic agents that can reduce sympathetic tone by acting on presynaptic receptors are being developed. Selective dilation of certain vascular beds may be possible with agents designed to interact with vascular dopaminergic receptors. The mechanisms whereby circulating epinephrine and norepinephrine modulate norepinephrine release and vascular tone are beginning to be understood and likely involve presynaptic, postsynaptic and nonsynaptic vascular receptors. A better appreciation of the mechanisms involved in the fine control of the peripheral circulation should allow for more selective and more imaginative pharmacologic therapy for CHF.

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Congestive heart failure (CHF) is a complex clinical syndrome that defies simple definition. The mechanisms underlying its pathophysiology are poorly understood and treatment is not uniform. Despite these uncertainties, new treatments continue to evolve. In the case of converting enzyme inhibitors, the long-term favorable effects of therapy confirm the suspicion that the renin-angiotensin-aldosterone system undoubtedly plays an important mechanistic role in CHF. Other vasoactive moieties, including plasma norepinephrine (NE) and arginine vasopressin (AVP), are also increased in CHF.[1] However, pharmacologic inhibition of NE[2,3] and AVP[4] as a form of treatment is more controversial and less well developed than the use of converting-enzyme inhibitors.

Early studies in patients with systemic hypertension and cirrhosis led to the belief that arginine vasopressin, aldosterone and angiotensin II are also important in the pathogenesis of CHF.[5] Likewise, it has been known for many years that the sympathetic nervous system is abnormal in CHF.[6] More recently the concepts of increased circulating norepinephrine,[7] reduced myocardial β-adrenergic receptor density[8] and reduced myocardial responsiveness to β-adrenergic stimulation[9] have offered new directions for research in CHF. This review presents an overview of the roles of the sympathetic nervous system and the renin-angiotensin-aldosterone system as well as arginine vasopressin in CHF and focuses on how such insight might be translated into more rational pharmacologic therapy.

Plasma Catecholamines, Renin Activity and Arginine Vasopressin

Congestive heart failure is characterized by high levels of circulating norepinephrine[10] and, in many cases, there is increased plasma renin activity (PRA)[10] and plasma AVP.[11] Plasma epinephrine is also sometimes increased, but this hormone is more often normal in the unstressed patient with CHF. Epinephrine, a true circulating hormone, is released from the adrenal medulla in response to stress. Norepinephrine, primarily

From the Departments of Medicine, University of Minnesota Medical School and the Veterans Administration Medical Center, Minneapolis, Minnesota. This study was supported by Grants HL22977-03 and HL07184, from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and a grant from the Veterans Administration Research Service, Washington, D.C.

Address for reprints: Gary S. Francis, MD, Director, Cardiovascular Research, Veterans Administration Medical Center, Minneapolis, Minnesota 55417.

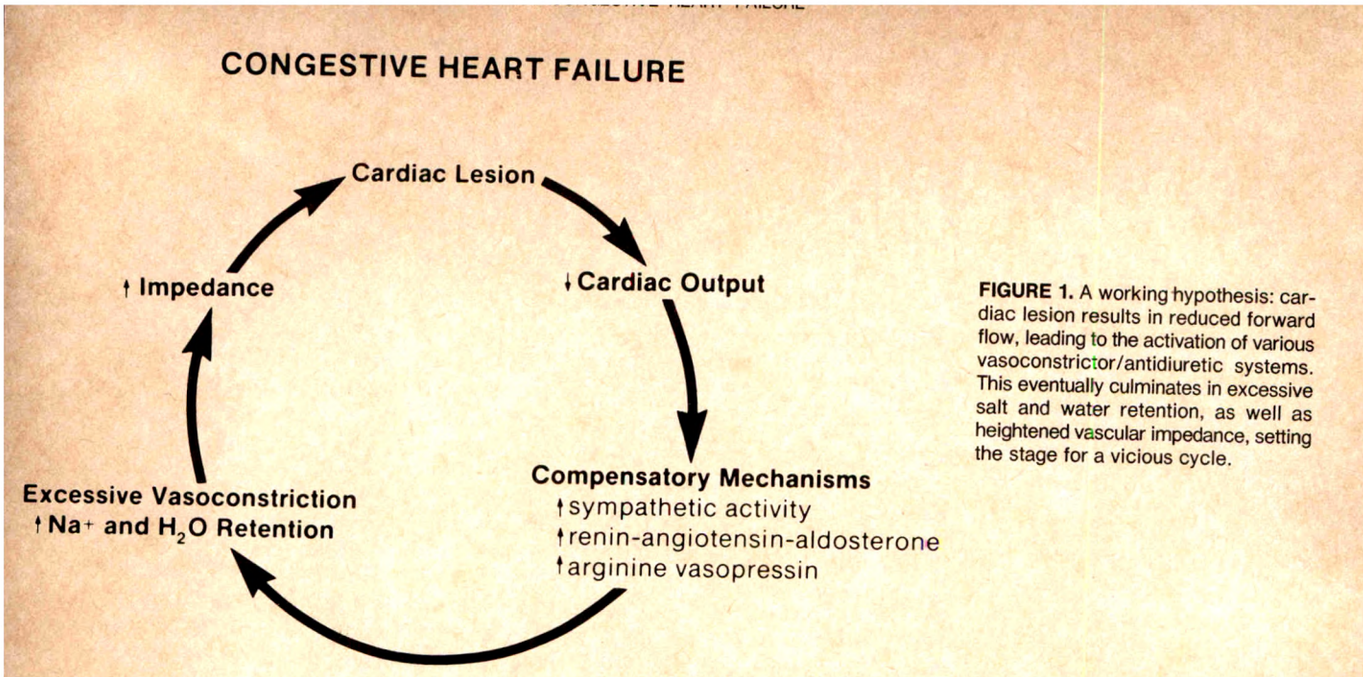

FIGURE 1. A working hypothesis: cardiac lesion results in reduced forward flow, leading to the activation of various vasoconstrictor/antidiuretic systems. This eventually culminates in excessive salt and water retention, as well as heightened vascular impedance, setting the stage for a vicious cycle.

a neurotransmitter, is not a circulating hormone, but is released from terminal sympathetic neurons during excitation of sympathetic nerves. It is generally agreed that venous plasma NE provides a useful index of average sympathetic nervous system activity.[12,13] What is not entirely clear is whether plasma NE, PRA and AVP actually contribute to the clinical syndrome of CHF in a biologically meaningful way. Do they offer support to the failing circulation or do they contribute a further burden to myocardium that is already operating inefficiently under an afterload stress (Fig. 1)?

The sympathetic nervous system and the endocrine system evolved as different systems devoted to coordination. The two systems overlap boundaries, although embryologically and phylogenetically they may have independent derivations.[14] It is presumed that sympathetic activity, PRA and AVP evolved as separate but interrelated functional units designed in part to maintain perfusion pressure and retain circulating volume in the face of inadequate blood flow.[15] The sympathetic nervous system, the renin-angiotensin system and AVP interact with each other. Angiotensin II, in addition to being an arteriolar constrictor and an important stimulus for the release of aldosterone, facilitates noradrenergic transmission in the autonomic nervous system.[16] Angiotensin II is also an acute stimulus for AVP release.[17] Arginine vasopressin potentiates the vasoconstrictor effects of NE and angiotensin II.[18] The hemodynamic effects of AVP are magnified when reflex control of the circulation is impaired,[19,20] and patients with CHF display a consistent abnormality of autonomic reflex control.[15] In normal unanesthetized dogs, arterial pressure does not increase substantially until plasma levels of AVP well in excess of the normal range are reached. In the absence of baroreceptor reflexes, the overall pressor sensitivity is enhanced 60- to 100-fold above normal.[21] Patients with CHF have a blunted baroreceptor response to upright tilt[22] and a reduced sinus node response to pressor injections.[23] They are perhaps more sensitive to increased circulating AVP, although this is still unproved. Reports comparing vasoconstrictor actions of various humoral agents indicate that AVP is the most potent circulating vasoconstrictor hormone studied to date.[24]

The precise signals that activate the sympathetic nervous system, the renin-angiotensin system and arginine vasopressin in CHF are unknown. They are probably under different control mechanisms, since the correlation coefficient between plasma NE and PRA in patients with heart failure is rather modest ($r = 0.38$).[10] The correlation between plasma AVP and plasma NE is also low ($r = 0.31$), as it is between AVP and PRA ($r = 0.53$).[11] Although these systems are probably under different control mechanisms, they facilitate each other's biologic activities and share the common properties of vasoconstriction and antidiuresis. This suggests that together they orchestrate a major defense system against inadequate perfusion from many causes, including inadequate cardiac output. The critical unanswered question is whether these systems act to "overcompensate" in CHF, resulting in circulatory congestion and heightened vascular impedance on a myocardium that is already operating under an imposed afterload stress. This may be the case, because inhibition of NE release by bromocriptine[25] and interruption of the renin-angiotensin system by converting-enzyme blockade[26] acutely improve the hemodynamic status of patients with CHF. As is often the case in clinical medicine, treatment may eventually yield further insight into mechanisms of the disease process itself.

Biosynthesis, Release and Biologic Activity of Norepinephrine—Vascular Neuroeffector Mechanisms and Interaction with Angiotensin II

Both the neurotransmitter norepinephrine and the hormone epinephrine are synthesized by chromaffin cells in the adrenal medulla and parts of the brain, whereas only NE is synthesized in the postganglionic

sympathetic nerves. The enzymes necessary to convert L-tyrosine to NE are present in the nerve ending, where the bulk of the NE is synthesized and stored (Fig. 2). Under normal circumstances L-tyrosine is transported from the blood across the membrane of the sympathetic nerves by a special concentrating mechanism. It is then acted upon by tyrosine hydroxylase to slowly produce L-dihydroxyphenylalanine (dopa). This is normally considered to be the rate-limiting step in the biosynthesis of NE.[27] Tyrosine hydroxylase activity is itself inhibited by NE, which is important in controlling NE synthesis.[28] Dopa is then rapidly decarboxylated in the terminal nerve to dopamine, which must then enter the small granulated vesicles, where it is finally hydroxylated by dopamine-β-hydroxylase (DBH) to NE. The NE is then stored until excitation of the sympathetic nerve results in exocytosis, a process whereby storage granules move, perhaps via microtubules, to the surface of the nerve membrane where they expel their contents into the synaptic cleft. Release of NE and DBH is enhanced by calcium ions and is inhibited to some extent by prostaglandin E_2. An important majority of the NE released by the nerve ending is taken back up into synaptic nerve terminals by active transport mechanisms (uptake 1). A lesser amount diffuses into the bloodstream, binds to postsynaptic receptors or is actively taken up by muscle tissue (uptake 2) and subsequently metabolized by catechol-o-methyl transferase and monoamine oxidase. The concentration of NE measured in plasma is therefore only a small fraction of what is released into the synaptic cleft, although it generally does reflect the amount of sympathetic activity.[13]

In patients with CHF[29] and in experimental animal models of heart failure,[30] the biosynthesis of NE is deranged. Patients with CHF have reduced myocardial stores of NE,[29] but may have increased myocardial dopamine content.[31] This is also true of certain animal models of heart failure. Syrian hamsters with hereditary cardiomyopathy cannot transfer dopamine efficiently across the membrane of the noradrenergic granule,[32] which could account for the 20-fold increase in dopamine content and the markedly reduced NE content of the myocardium in this model. This essentially shifts the rate-limiting step of NE biosynthesis from hydroxylation of tyrosine to the hydroxylation of dopamine. The mechanism of reduced transport of dopamine across vesicular membranes is uncertain, but could be due to an acid pH in the nerve terminal cytoplasm, allowing for protonation and subsequent poor membrane transportability of dopamine.[33] High-energy phosphate depletion could also account for this mechanism, because this transport is dependent on magnesium-activated adenosine triphosphate.[34]

The release of NE from postganglionic neurons is complex and incompletely understood. It is likely that many presynaptic receptors can facilitate or inhibit NE release. These include the presynaptic α_2 receptor, the presynaptic β_2 receptor, the presynaptic dopamine (DA_2) receptor, and the presynaptic angiotensin II receptor (Fig. 3). Although there is still controversy regarding the actual presence and activity of these various receptors on neurons, data have emerged that generally

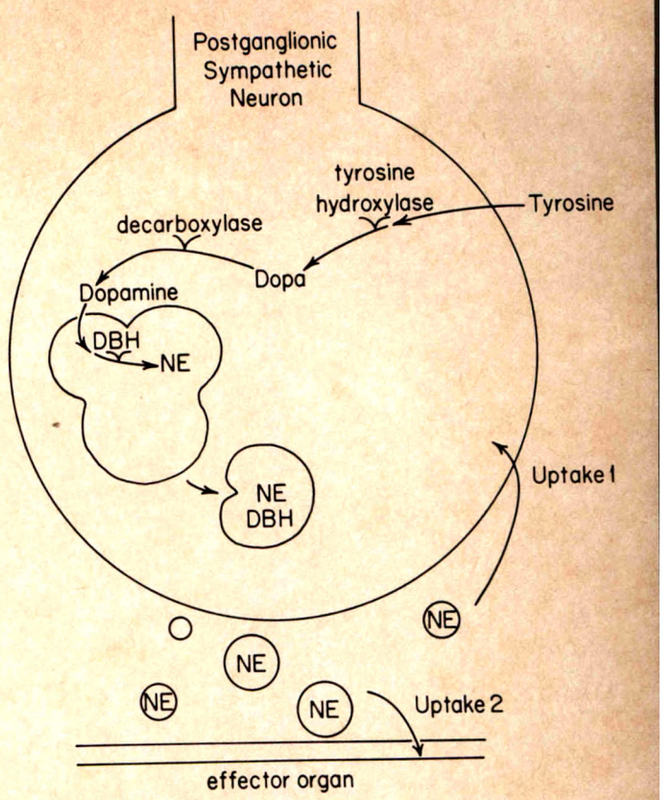

FIGURE 2. Biosynthesis, storage and release of norepinephrine (NE) from terminal sympathetic neuron. A potential lesion in heart failure may be the inability to transport dopamine from the cytoplasm to the vesicle, resulting in a reduced NE level and increased dopamine myocardial content. DBH = dopamine-β-hydroxylase.

support the concept of multiple controls over the release of NE from sympathetic nerves. Presynaptic α_2 receptors are believed to be located on membranes of sympathetic neurons.[35] When the presynaptic α_2 receptor is engaged by an endogenous agonist such as NE, or a pharmacologic agonist such as clonidine, guanabenz or guanfacin, NE release is inhibited.[36] With NE, this mechanism likely serves a negative feedback system that partially regulates sympathetic drive. Presynaptic neuronal β receptors are also likely to be present[37] and they appear to facilitate NE release when stimulated by an agonist such as epinephrine or NE.[38] The presynaptic β adrenoceptors are probably of the β_2 variety[39] and are therefore likely to be more responsive to epinephrine than NE. Like the presynaptic α_2 receptor, the presynaptic DA_2 receptor subserves inhibition of NE release from postganglionic sympathetic nerves in response to nerve stimulation.[40]

Although there are a large number of pharmacologic DA_2 agonists, the two that have been used to blunt high sympathetic drive in patients with CHF are bromocriptine[25] and propylbutyldopamine.[41] Bromocriptine inhibits NE release,[42,43] and this effect may be mediated through a central dopaminergic rather than a peripheral mechanism.[44] Angiotensin II receptors also occur on presynaptic sites where, like β receptors, they facilitate the release of NE.[45,46] In addition to presynaptic α_2, β_2, DA_2 and angiotensin II receptors, presynaptic inhibitory muscurinic and opiate receptors have also been

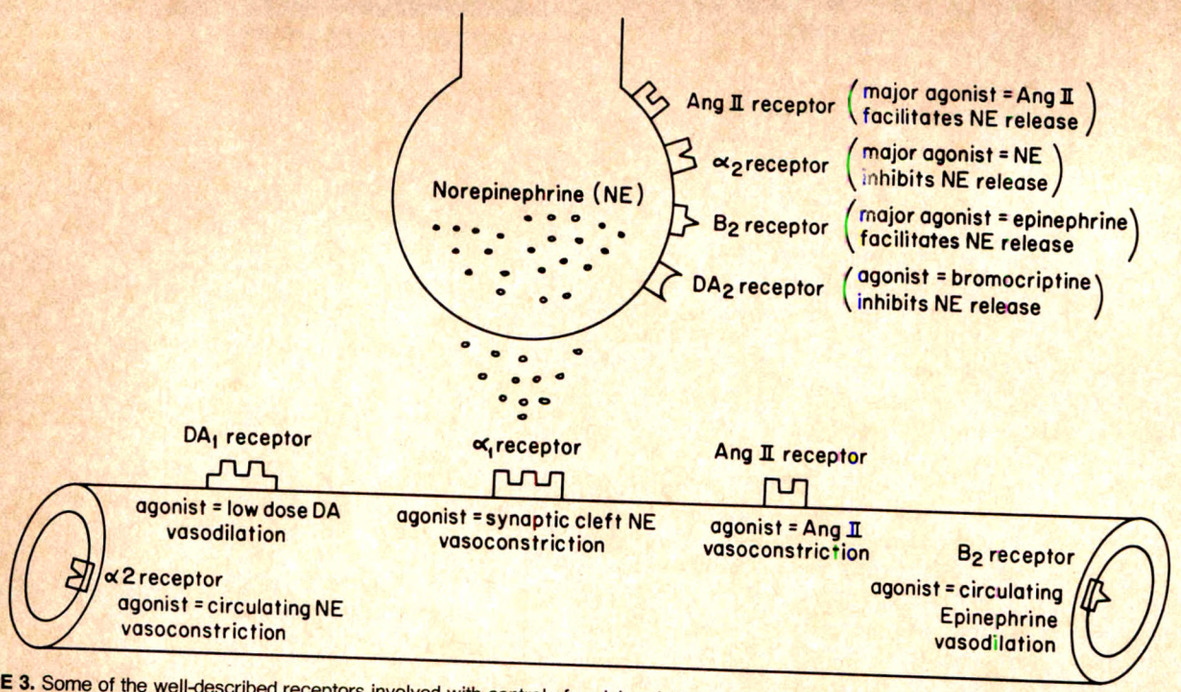

FIGURE 3. Some of the well-described receptors involved with control of peripheral circulation. Presynaptic DA_2 and α_2 receptors subserve inhibition of norepinephrine (NE) release, while presynaptic angiotensin II (Ang II) and β_2 receptors subserve facilitation of NE release. On the vascular side, postjunctional α_2 receptors are near the lumen and are sensitive to circulating catecholamines. They subserve vasoconstriction. Postjunctional β_2 receptors are similarly remote from the synaptic cleft and subserve vasodilation. The postsynaptic α_1 receptor responds to neuronal release of NE with vasoconstriction. Vascular DA_1 and angiotensin II receptors subserve vasodilation and vasoconstriction, respectively. The DA_1 receptor is responsive to circulating substances such as low-dose dopamine and SKF 82526.

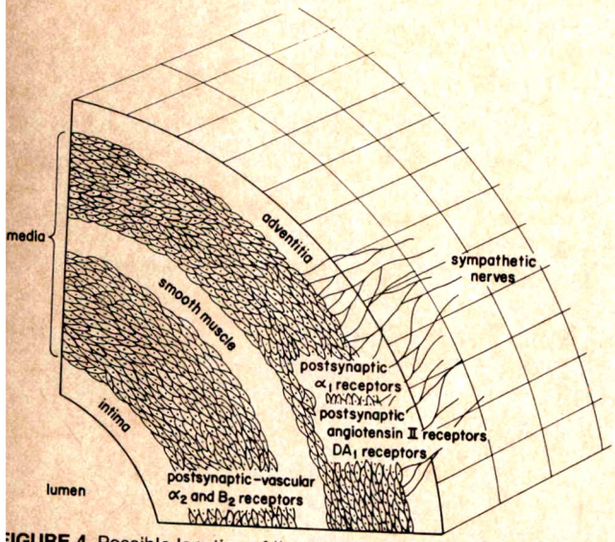

FIGURE 4. Possible location of "postsynaptic" vascular receptors that may be amenable to pharmacologic therapy in congestive heart failure. The vascular postjunctional α_2 and β_2 receptors are remote from the synaptic cleft and are likely more responsive to circulating or blood-borne catecholamines. Postsynaptic α_1 receptors are in close proximity to synaptic cleft and are responsive to neuronally released norepinephrine, resulting in vasoconstriction. Postjunctional α_2 receptor modulates vasoconstriction, and postjunctional β_2 receptor modulates vasodilation. The actual location of vascular angiotensin II receptors, which promote vasoconstriction, is not entirely clear. The precise location of extrajunctional DA_1 receptor, which produces vasodilation, is also not entirely clear, but it seems responsive to circulating or blood-borne low concentrations of dopamine, as well as to pharmacologic agent SKF 82526.

described.[47] Additionally, inhibition of NE release by prostaglandins of the E series may be linked to specific presynaptic receptors.[48] Metabolic changes in the vicinity of the adrenergic neuroeffector junction can also decrease the output of neurotransmitter, including adenosine, potassium, hyperosmolality and the hydrogen ion.[49] Knowledge of the interaction of these multiple presynaptic receptors and their modulator activity is obviously incomplete, but fine pharmacologic control of sympathetic tone by use of converting-enzyme inhibitors and selective DA_2 agonist may be useful to reduce the heightened sympathetic drive present in CHF. Such fine control may contribute to an improved clinical state.

At least 5 putative postsynaptic vascular receptors have been identified (Fig. 3), and information about them is rapidly increasing.[35] The postsynaptic α_1 receptor is sensitive to neuronally released NE and responds with vasoconstriction. It is present on both arterioles and veins, although deep veins in the skeletal muscles have little or no sympathetic innervation. The α_1 postsynaptic receptors are located in smooth muscle adjacent to nerve varicosities at the interface of the adventitia and the media (Fig. 4). The vascular α_2 receptors are located extrajunctionally, closer to the lumen, at some distance from the nerve terminal,[50] and are more responsive to exogenous or circulating epinephrine and NE.[35] The vascular α_2 receptors are present in both veins and resistance vessels and mediate vasoconstriction. Circulating epinephrine is slightly

more potent than NE at vascular α_2 receptors.[50] It is of interest that calcium antagonists cause a significant reduction of the vasoconstrictor response induced by selective vascular α_2 agonists.[51] Calcium entry blockers do not interfere with the formation of the vascular α_2-agonist/receptor complex, but they may prevent the influx of extracellular calcium ions associated with activation of the α_2 receptor. Some of the vasodilator properties of calcium blockers may be related to this mechanism. Vascular β adrenoceptors are similarly remote from the synaptic cleft and are also more sensitive to circulating rather than neuronally released catecholamines. The vascular β receptors modulate vasodilation rather than vasoconstriction. It is unclear if vascular β receptors are present on veins, but they have been convincingly demonstrated in arterial vessels,[52] where they are probably of the β_2 variety.[53] Vascular postsynaptic DA_1 receptors have been identified in the renal, mesenteric, coronary and cerebral circulations, where they are known to modulate vasodilation.[54] The DA_1 receptor agonist dopamine is sometimes clinically used in small doses to promote renal artery vasodilation and saluresis in patients with CHF. Preliminary data suggest that SKF 82526, an oral synthetic DA_1 agonist, may have potential use in CHF by increasing renal blood flow and enhancing natriuresis.[55] Smooth muscle arteriolar vasculature also contains postsynaptic angiotensin II receptors.[46] Angiotensin II interacts directly with this receptor to promote vasoconstriction. An adrenergic potentiating effect of angiotensin II on smooth muscle also appears to be attributable to a postsynaptic action.[56]

Angiotensin II, like NE, plays a pivotal role in control of peripheral circulation. Angiotensin II facilitates NE release through a presynaptic receptor mechanism, promotes vasoconstriction directly through a postsynaptic receptor, blocks neuronal uptake of NE,[57] enhances NE biosynthesis in the adrenergic nerve terminal,[58] releases epinephrine from the adrenal medulla,[59] acts on the adrenal cortex to release aldosterone, augments the vascular smooth muscle response to various agonists and probably stimulates central NE activity as well. Thus, it is not unexpected that in patients with CHF in whom the converting-enzyme activity is blocked, both sympathetic tone and salt and water retention are reduced. It is also possible that high concentrations of converting-enzyme inhibitor act directly to block the α-adrenergic responsiveness in vascular smooth muscle.[60] Converting-enzyme-inhibiting drugs, therefore, may act through multiple mechanisms in patients with CHF (Table I).

Several analogs of angiotensin II have been developed for diagnostic and therapeutic purposes,[61] including Sar^1 Ala^8 angiotensin II, which acts as partial competitive inhibitor or agonist at the postsynaptic vascular receptor site. When circulating levels of endogenous angiotensin II are elevated, Sar^1 Ala^8 angiotensin II will displace endogenous angiotensin II from the receptor, resulting in a net vasodilator antagonist effect. When receptor occupancy is low, such as during converting enzyme activity treatment, this analog acts as an agonist, mimicking the pressor effects of endogenous angiotensin II. Therefore, it could be used to treat severe hypotension resulting from excessive converting enzyme activity therapy.

TABLE I Potential Mechanisms of Converting Enzyme Inhibitors in Patients with Heart Failure

Inhibition of A_{II} formation resulting in arteriolar dilation
Inhibition of A_{II} formation resulting in reduced aldosterone production
Inhibition of A_{II} formation resulting in reduced NE release
Inhibition of A_{II} formation resulting in "densensitization" of vascular tissue to constrictor substances
Inhibition of A_{II} formation resulting in ↓NE biosynthesis
Inhibition of brain A_{II} formation resulting in ↓CNS sympathetic activity
Inhibition of A_{II} resulting in improved right ventricular-pulmonary vasculature compliance
Direct α_1 adrenergic vascular receptor blockade (requires large doses in vitro)
Increase in local prostaglandin production with venodilation

A_{II} = angiotensin II; NE = norepinephrine; CNS = central nervous system.

Although the preceding description of adrenergic and angiotensin receptor activity is undoubtedly oversimplified and subject to change, a basic understanding of these processes may be useful for clinicians caring for patients with CHF. Progress in the pharmacologic control of peripheral circulation is rapidly evolving, and future directions may include many different agents that can selectively activate or block various receptor activities. Table II lists what is known about the control of the peripheral circulation by certain receptors. Undoubtedly, other receptors responsive to acetylcholine, serotonin, AVP and others are also important in this regard, but their pharmacologic control has not been explored in CHF.

Arginine Vasopressin in Congestive Heart Failure

Until recently, the antidiuretic hormone AVP has not been well studied in patients with CHF, in part because of the lack of reliable assay techniques. An early report using a bioassay did suggest, however, that vasopressin may sometimes be abnormally increased in patients with CHF.[62] The availability of a sensitive and specific radioimmunoassay with an intraassay coefficient of variation of less than 4% has allowed investigators to detect changes in plasma vasopressin as small as 0.2 pg/ml.[63] Although the increase in circulating AVP in patients with CHF is neither as uniform nor as striking as that of plasma NE and PRA, on average there is about a 2-fold increase in circulating AVP in most patients.[11] The precise mechanism of increased AVP in heart failure, as with plasma NE and PRA, is not well understood. Increased angiotensin II could stimulate release of AVP,[17] but as previously noted, the correlation between PRA and AVP is only modest ($r = 0.53$). Moreover, captopril given acutely fails to lower AVP in patients with CHF.[11] Digitalis therapy, if it had any effect, would tend to lower AVP levels.[64] AVP may not be cleared adequately by the liver and kidneys in patients with CHF, but an increase in levels is observed even in patients who demonstrate normal hepatic and renal function.[11] Abnormalities of osmotic control are more likely to be involved, because patients with CHF

TABLE II Neuronal and Vascular Receptors Linked to Control of the Peripheral Circulation

Receptor	Location	Agonist	Antagonist	Biological Activity	
				Agonist	Antagonist
α_2 adrenergic	Neuronal (central, peripheral)	NE Clonidine Guanabenz Guanfacin α-methyldopa metabolite	Yohimbine Rauwolscine	↓NE release	↑NE release
α_2 adrenergic	Vascular	Epinephrine NE (circulating)	? Calcium channel blockers (indirect)*	Vasconstriction	Vasodilation
DA_2	Neuronal (central, ganglionic, peripheral)	Dopamine Bromocriptine Propylbutyldopamine	Metaclopramide S-sulpiride	↓NE release ↓Prolactin	Antiemetic
DA_1	Vascular (renal, mesenteric, coronary, cerebral)	Dopamine (small dose) SKF 82526	R-sulpiride Haloperidol	Vasodilation Natriuresis	
α_1 adrenergic	Vascular	NE (neuronal)	Prazosin	Vasoconstriction	Vasodilation
Angiotensin II	Neuronal	Angiotensin II	Converting enzyme inhibitors (indirect)*	↑NE release	↓NE release
Angiotensin II	Vascular	Angiotensin II	Saralasin (partial agonist)	Vasoconstriction	Vasodilation
β_2 adrenergic	Neuronal	Epinephrine NE	Propranolol Timolol	↑NE release	↓NE release
β_2 adrenergic	Vascular	Epinephrine NE (circulating) Dobutamine	Propranolol Timolol	Vasodilation	Vasoconstriction

* Calcium channel blockers and converting-enzyme inhibitors do not interact directly with α_2 receptors and therefore are not α_2 receptor "antagonists" in the usual sense. See text for explanation.
NE = norepinephrine.

lack the usual good correlation between serum sodium and AVP. Low serum sodium may coexist with high AVP levels in patients with CHF, but increased vasopressin does not always result in hyponatremia. We have observed that these patients do not suppress their AVP with water loading to the same extent as normal subjects do. In the absence of frank hypotension, a reduction in filling pressure with nitroprusside fails to stimulate AVP in heart failure, suggesting that intracardiac baroreceptor reflexes are not very important in the fine-control mechanisms of AVP release. Despite our uncertainty regarding the mechanism of AVP increase in patients with CHF, we believe that it may be contributing to heightened vascular resistance and water retention. The development of selective blockers of the vascular and renal effects of vasopressin may allow this hypothesis to be tested.

In conclusion, treatment for patients with CHF is rapidly evolving. Important new information about the mechanism of peripheral vascular control has led to the belief that fine control of these systems may be possible. The development of the converting-enzyme inhibitors is an excellent example of how basic science can quickly translate into established treatment when the need is pressing. Perhaps more importantly, a firmer understanding of the control of peripheral circulation has been made possible by the work of many basic pharmacologists and clinical investigators. The era of simply prescribing a "vasodilator" for CHF is over. Highly selective agents with the potential for much finer control of circulation will become available. The use of such selective agents may not only result in more rational treatment for CHF, but may ultimately expand our understanding of some very basic processes related to control of peripheral circulation.

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Cardiopulmonary Exercise Testing for Evaluation of Chronic Cardiac Failure

KARL T. WEBER, MD, and JOSEPH S. JANICKI, PhD

The heart, lungs and hemoglobin form the body's gas transport system, which links the atmosphere and its supply of O_2 with tissue, while simultaneously providing for the elimination of the metabolic end-product, CO_2, into the atmosphere. The transport of these respiratory gases must be in accordance with metabolic need. This is particularly evident during the physiologic stress of isotonic exercise, when the O_2 requirements and CO_2 production of skeletal muscle are increased. The monitoring of these respiratory gases during exercise, referred to as cardiopulmonary exercise testing (CAR-PET), can be used to assess heart and lung function in patients with cardiovascular or lung disease or both. Chronic cardiac failure (CCF) may be defined in physiologic terms as that circumstance in which the heart fails to provide tissue with O_2 at a rate commensurate with aerobic requirements. In patients with CCF, CAR-PET represents a noninvasive means to determine aerobic capacity (that is, maximal O_2 uptake) and anaerobic threshold during incremental treadmill exercise. It can also provide an objective measure of the severity of failure, the functional status of the patient and the heart's pump reserve. By using additional measurements of ventilation, arterial O_2 saturation and, in selected cases, hemodynamic monitoring, the nature and severity of cardiovascular and pulmonary disease may be evaluated.

(Am J Cardiol 1985;55:22A–31A)

The severity of chronic cardiac failure (CCF) has traditionally been gauged according to the extent of breathlessness or fatigue, or both, and the extent to which these symptoms limit effort tolerance. In an attempt to overcome such subjective and therefore frequently unreliable information, various expressions of ventricular function have been used. However, the relation between effort tolerance and such measurements as ejection fraction, cardiac output and left ventricular filling pressure, each of which is obtained in the resting state, is poor.[1–6] Similarly, the heart's pumping reserve, or maximum cardiac output, which reflects the severity of CCF in physiologic terms, cannot be predicted from these measurements of ventricular function.[5,7] A more reliable and objective estimate of patients' functional status and pump reserve is needed.

Determination of a patient's aerobic capacity and anaerobic threshold by the noninvasive measurement of respiratory gas exchange during incremental treadmill exercise provides such information.[5] In addition, it identifies aerobic and anaerobic levels of work for each patient. Combined with the measurement of air flow, this approach can be used to distinguish ventilatory from circulatory causes of exertional dyspnea.[8] Over the years we have relied heavily on this approach, which we term cardiopulmonary exercise testing (CAR-PET), for 3 purposes: to examine the severity of CCF, to determine the efficacy of various therapeutic interventions in patients with CCF,[9–12] and to evaluate the pathophysiologic responses associated with the appearance of exertional dyspnea or fatigue. In selected patients, we also monitor arterial O_2 saturation or intravascular hemodynamics, or both, to elucidate the pathophysiologic mechanisms of effort intolerance.[5,8,13] This report discusses CAR-PET and identifies how this relatively new approach can assist cardiologists in the evaluation and management of CCF.

From the Cardiology Section, Department of Medicine, Michael Reese Hospital & Medical Center, University of Chicago, Chicago, Illinois. Address for reprints: Karl T. Weber, MD, Cardiology Section, Michael Reese Hospital & Medical Center, Lake Shore Drive at 31st Street, Chicago, Illinois 60616.

The Physiologic Basis of CAR-PET

The body's gas transport system—the cardiopulmonary unit: The chemical source of energy that allows cells to derive the means necessary to sustain their many functions, including life itself, is the oxidation of carbohydrates and fats. Oxidation is the biochemical process by which electrons, derived from the breakdown of glucose and fats, are transferred from

hydrogen to O_2 to form water. Oxygen is the final acceptor of these electrons. It is therefore critical that the cells be linked to the atmosphere and its supply of O_2 to sustain oxidative metabolism. The heart and lungs, together with hemoglobin, form the body's gas transport system. At the same time that oxidative metabolism consumes O_2 ($\dot{V}O_2$), CO_2 is being produced ($\dot{V}CO_2$). The amount of CO_2 produced by oxidation is considered the *metabolic* source of CO_2[14] and is a function of the proportion of carbohydrates and fats utilized by the cells. Normally, 75 to 80 ml of CO_2 are produced for every 100 ml of O_2 consumed. The ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ is termed the respiratory gas exchange ratio (R); R normally equals 0.75 to 0.80. Because an acidosis will occur if CO_2 accumulates in the body, the cells must again be linked to the atmosphere to provide for CO_2 elimination. The heart and lungs provide for CO_2 transport and its elimination into the atmosphere. Accordingly, the heart and lungs may be viewed as an integrated, metabolic unit designed to maintain O_2 and CO_2 transport and exchange; neither organ can function independently in meeting this objective. We term this respiratory gas transport system the "cardiopulmonary unit."[15]

The cardiopulmonary unit is placed under a considerable demand during isotonic exercise as the $\dot{V}O_2$ of exercising muscle and the $\dot{V}CO_2$ rise in proportion to the level of muscular work performed. O_2 availability must be matched to $\dot{V}O_2$. The integrity of the unit and the precision with which the heart and lungs provide O_2 and eliminate CO_2 can therefore be scrutinized during exercise. A defect in heart or lung function may first become apparent during the physiologic stress of exercise. Hence, in physiologic terms, CCF may be defined as that condition in which the heart cannot provide O_2 to tissue at a rate commensurate with aerobic requirements. In patients with severely advanced heart disease, CCF may be apparent at rest when $\dot{V}O_2$ is only 1 metabolic equivalent (3.5 ml/min/kg of dry body weight). With less severe disease, the defect in O_2 delivery may only become apparent as $\dot{V}O_2$ rises during physical activity.[16]

Years ago, the late Louis N. Katz[17] emphasized that the heart's inability to deliver O_2 could be secondary to a variety of disorders, and thus one must distinguish the cause. Cardiac output, for example, could be inadequate because of a *myocardial* defect (e.g., myocardial infarction or cardiomyopathy) or a nonmyocardial or *circulatory* cause (e.g., hypovolemia, mitral stenosis, occlusive pulmonary vascular disease or constrictive pericarditis). In this review we discuss patients with chronic cardiac failure, secondary to coronary heart disease or dilated cardiomyopathy.

Concepts of O_2 delivery and O_2 utilization: O_2 delivery in ml/min is the rate at which O_2 is transported to the tissues. O_2 delivery is equal to the product of cardiac output and the arterial O_2 content, and O_2 content is related to the concentration of hemoglobin, its degree of O_2 saturation and its O_2 combining capacity. The normal arterial O_2 content is 19 ml/100 ml, or 14 g/100 ml · 95% · 1.34 ml/g. A certain amount of the O_2 delivered to the capillaries is extracted by tissue. O_2 extraction is therefore expressed as the ratio of the arteriovenous O_2 difference to the arterial O_2 content. Because the amount of hemoglobin in venous blood is essentially no different from arterial blood, the amount of O_2 that leaves the capillaries will be represented by the O_2 saturation of venous blood. Therefore, venous O_2 saturation is a function of O_2 delivery and O_2 extraction. In the mixed venous blood of the pulmonary artery, O_2 saturation is a function of systemic blood flow and the body's overall extraction of O_2.

Oxygen delivery and O_2 extraction will be related to O_2 utilization, or the rate of O_2 consumption per unit time. To simplify this relation (i.e., by factoring out arterial O_2 content), $\dot{V}O_2$ is equal to the product of cardiac output and the arteriovenous O_2 difference. This is another version of Adolph Fick's theorem. At rest, $\dot{V}O_2$ averages 245 ml/min for a 70-kg person while O_2 delivery equals 950 ml/min (i.e., 5,000 ml/min of blood flow · 19 ml/100 cc of blood). Thus, there is more than an adequate supply of O_2 to satisfy $\dot{V}O_2$; as a result, systemic O_2 extraction averages 25%.

Cardiopulmonary and tissue reserves: The $\dot{V}O_2$ of the body's organs varies widely and differs from the percentage of systemic blood flow they receive. Moreover, the need for O_2 varies among tissues throughout the day according to physiologic priorities (e.g., walking, digestion, sweating). The heart and lungs must be able to respond to each of these demands and ensure O_2 transport relative to need. During muscular work, for example, $\dot{V}O_2$ increases. Minute ventilation ($\dot{V}_E$) and O_2 delivery must each increase proportionately and at a rate appropriate to sustain oxidation metabolism. With strenuous work, $\dot{V}_E$ increases to 8 times or more its level at rest. Rarely does $\dot{V}_E$ pose a limitation to sustaining aerobic work.[18] The ventilatory reserve available for exercise is reflected in the maximum voluntary ventilation (MVV) and the forced vital capacity (FVC) measured during routine pulmonary function testing. Exercise $\dot{V}_E$ constitutes some fraction of the MVV, while the exercise tidal volume occupies some fraction of the FVC. Normally, less than 50% of the MVV and FVC is used to respond to the ventilatory requirements of light, moderate and moderately heavy workloads.[19]

The heart's pump reserve is not as great as its ventilatory reserve. In an untrained person cardiac output will rarely increase more than 4- or 5-fold above its rest value with strenuous work. Thus, unlike the lungs, the heart poses a limitation to aerobic work. The final reserve to gas transport exists within the tissue and is related to its ability to raise the level of O_2 extraction and to vasodilate the circulation. This represents the tissue reserve. Together, the response in cardiac output and the ability of muscle to extract O_2 and vasodilate determine a person's aerobic capacity, or maximal $\dot{V}O_2$ ($\dot{V}O_2$ max).[20] $\dot{V}O_2$ max can therefore be equated to maximum O_2 delivery and maximum O_2 extraction. In the averaged-sized, middle-aged person, whose maximal cardiac output is 20 liters/min and whose maximum level of O_2 extraction is 75%, representing an arteriovenous O_2 difference of 14 ml/100 ml, $\dot{V}O_2$ max equals 2,800 ml/min or 40 ml/min/kg. $\dot{V}O_2$ max varies according to sex, age and physical training.[21] Furthermore,

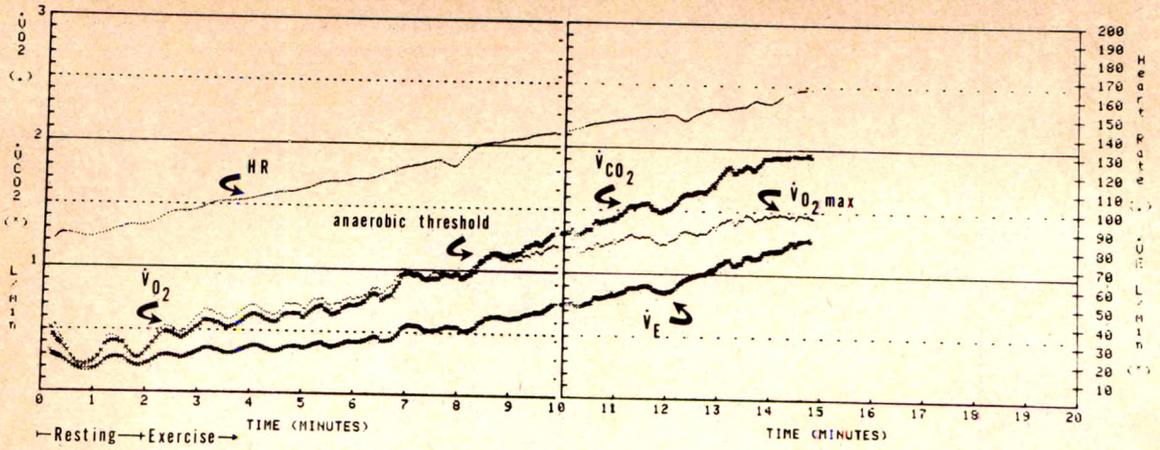


FIGURE 1. Breath-by-breath response in O_2 uptake ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) to incremental (2-minute stages) treadmill exercise in a 65-year-old man with enlarged heart and mitral valve incompetence. Appearance of anaerobic metabolism is indicated by crossover in $\dot{V}O_2$ and $\dot{V}CO_2$; the corresponding $\dot{V}O_2$ is termed anaerobic threshold. Maximal O_2 uptake ($\dot{V}O_2$ max) is achieved when $\dot{V}O_2$ fails to increase more than 1 ml/min/kg after an increment in treadmill work. Heart rate (HR) response is also shown.

the $\dot{V}O_2$ max achieved for a particular muscle group or for a specific form of exercise should not be compared to other muscle groups or other forms of physical activity.[22] Treadmill exercise, for example, yields the largest $\dot{V}O_2$ max in normal subjects; thus, it should not be compared to the $\dot{V}O_2$ max measured during exercise on a bicycle ergometer or with arm exercise.

Muscular work and $\dot{V}O_2$ may increase more quickly or to the extent that the cardiocirculatory system can provide adequate O_2. Consequently, O_2 availability will be inadequate. In such cases, working skeletal muscle will resort to less efficient, anaerobic pathways to derive its energy. Anaerobic muscle produces lactate, which, because of its low dissociation constant, is rapidly buffered by bicarbonate. As a result of lactate buffering, an additional, *nonmetabolic* source of CO_2 is produced and R must rise above 0.75–0.80.[14] To maintain eucapnia under these circumstances, $\dot{V}_E$ must also increase. These variations in respiratory gases and $\dot{V}_E$ can be used to detect the onset of anaerobic metabolism during isotonic exercise and corresponding level of work, or $\dot{V}O_2$ associated with anaerobiosis. This event is termed the "anaerobic threshold."[23]

Types of CAR-PET

Noninvasive incremental treadmill exercise test: The availability of rapidly responding O_2 and CO_2 analyzers has made it possible to monitor these 2 respiratory gases on-line throughout exercise. These measurements, together with measurements of respiratory air flow, allow noninvasive determinations of $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, respiratory rate and tidal volume in response to isotonic muscular work. The heart rate, electrocardiogram and cuff blood pressure should also be monitored, as is the standard practice in cardiology.

We chose a program of gradually progressive (2-minute stages), upright, treadmill exercise[9] for our patients with CCF. We did so because walking represents a nonspecialized skill that is easily negotiable, reproducible and reliable; at the same time, walking works a muscle mass large enough to stress the cardiopulmonary unit. By monitoring respiratory gas exchange and air flow we can determine the anaerobic threshold and $\dot{V}O_2$ max of these patients during a single exercise test.[5] We define $\dot{V}O_2$ max as $\dot{V}O_2$ remaining invariant (≤1 ml/min/kg) despite an increment in workload sustained for 30 seconds or more. Anaerobic threshold has been defined according to several criteria, including disproportionate increase in $\dot{V}CO_2$, $\dot{V}_E$ and R relative to $\dot{V}O_2$ and disproportionate rise in end tidal O_2 relative to end tidal CO_2. Figure 1 depicts the $\dot{V}O_2$ max and anaerobic threshold for a 65-year-old man with a dilated heart and mitral valve incompetence. We do not attempt to define the absolute time in which anaerobiosis occurs; only the stage of exercise and the corresponding level of work. We have found that $\dot{V}O_2$ max and anaerobic threshold are reproducible in these patients and that the anaerobic threshold occurs at approximately 60% or more of their aerobic capacity.[5] Over the past 10 years we have safely and reliably obtained this information in hundreds of patients with CCF, and in many of these patients the test has been performed serially over several years to monitor the natural course of their disease or their response to medical therapy. We have specifically excluded testing patients with aortic stenosis, exertional angina, significant arrhythmia or exercise-induced arrhythmia.

Finally, an indirect, noninvasive method of monitoring arterial O_2 saturation, the ear oximeter, can be used as part of this test. This is a particularly useful screening procedure in cases where O_2 desaturation might be anticipated (e.g., restrictive lung disease or pulmonary vascular disease). We find that patients with CCF do not have a significant fall in O_2 saturation during exercise.[5] The technique, however, can give erroneous information in the black patient because of pigmented skin. In cases where O_2 desaturation is suspected or evident from noninvasive monitoring, arterial O_2 saturation should be measured directly.

Invasive incremental treadmill exercise test:

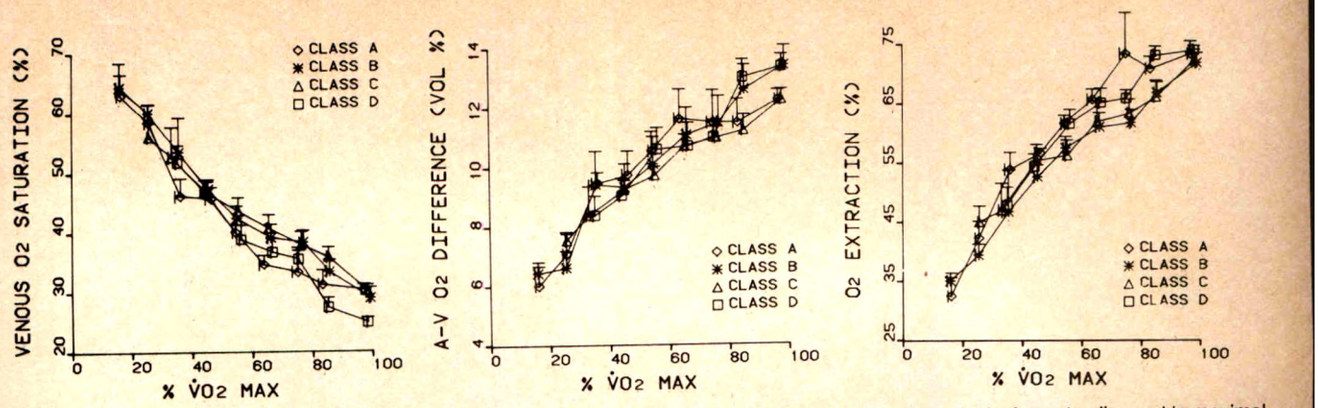


FIGURE 2. Response in mixed venous O_2 saturation, arteriovenous (A-V) O_2 difference and O_2 extraction, respectively, from standing rest to maximal exercise as a function of the normalized aerobic capacity (% $\dot{V}O_2$ max) for class A to D patients with chronic cardiac failure. Values of these parameters, observed for standing rest, are slightly different from those usually seen in supine rest and can be explained by reduction in cardiac output that occurs in standing position.

When myocardial failure needs to be differentiated from circulatory failure or when the severity of mitral apparatus dysfunction needs to be assessed, we monitor both the hemodynamic response and the gas exchange response to upright treadmill exercise.[5] For this test a triple-lumen flotation catheter with thermister is advanced via an arm vein into the terminal portion of the pulmonary circulation to obtain pulsatile pulmonary artery and occlusive wedge pressures with minimal catheter whip during each stage of exercise. Right atrial pressure can be similarly obtained through the proximal port of the catheter. We can also sample mixed venous blood for its O_2 saturation, and subsequently determine cardiac output by Fick principle and lactate concentration at each stage of exercise. Cardiac output by the thermodilution principle can also be determined during each stage. Advances in fiberoptic technology now make it possible to monitor mixed venous O_2 saturation on a continuous basis with a flotation catheter.[24] Finally, a catheter inserted into the radial or brachial artery of the same arm permits us to monitor arterial pressure directly and to sample arterial blood for its O_2 saturation and CO_2 tension if desired.

The Noninvasive Incremental Exercise Test in Evaluating the Severity of CCF

Maximum O_2 uptake: As noted earlier, $\dot{V}O_2$ max is a function of the maximum cardiac output that the heart can generate and the maximal amount of O_2 that the tissue can extract. We have assigned the aerobic capacity observed during an incremental treadmill exercise test into one of 4 classes, each of which represents a given degree of impairment.[5]

We termed the classes A, B, C and D to avoid confusion with the New York Heart Association classification.

Functional class A represents little or no impairment in aerobic capacity and is present when $\dot{V}O_2$ max exceeds 20 ml/min/kg. For age- and sex-corrected $\dot{V}O_2$ max of the normal adult population commonly seen in practice, $\dot{V}O_2$ max will be above this level. *Class B* represents mild-to-moderate impairment and is present when $\dot{V}O_2$ max ranges from 16 to 20 ml/min/kg. *Class C* represents moderate-to-severe impairment, and is present when $\dot{V}O_2$ max falls between 10 and 15 ml/min/kg. *Class D* represents a severe impairment, with a $\dot{V}O_2$ max of <10 ml/min/kg. The duration of treadmill exercise is far less precise in characterizing aerobic capacity and suffers from lack of an objective, quantitative endpoint to predict aerobic capacity. The predicted maximum heart rate is also imprecise in predicting $\dot{V}O_2$ max.[25] Moreover, exercise time is clouded by patient and physician bias. Finally, $\dot{V}O_2$ max correlates poorly with the New York Heart Association classification,[5] again emphasizing the subjective nature of clinical information.

To determine if impairment in aerobic capacity in patients with CCF is due to a compromised cardiac output response to exercise, inability of the tissues to extract O_2, or both, we monitored the response in mixed venous O_2 saturation, cardiac output, intravascular pressures and respiratory gas exchange during incremental treadmill exercise in 76 patients with CCF of varying severity (6 class A, 11 class B, 25 class C and 34 class D). Figure 2 shows the response in mixed venous O_2 saturation (SvO_2) from standing rest to maximum exercise in all classes of patients. We normalized $\dot{V}O_2$ at rest and during exercise according to $\dot{V}O_2$ max; i.e., each aerobic capacity was set equal to 100% and values less than $\dot{V}O_2$ max are equal to some fraction of the maximum. From its standing resting value, SvO_2 follows a common course, becoming progressively lower as O_2 extraction increases with higher workloads. At $\dot{V}O_2$ max, SvO_2 is 30% or less and there are no differences among classes. The same response, of course, is true for arteriovenous O_2 difference, which rises to 12 ml/100 ml or greater at maximal exercise and corresponds to an O_2 extraction in excess of 70% in each class. These data indicate that O_2 extraction increases progressively throughout exercise. The measurement of O_2 saturation and O_2 content in the femoral venous circulation of exercising leg indicate that O_2 extraction actually exceeds 80%.[26] The lesser value for O_2 extraction noted in mixed venous blood represents the dilutional effect of venous blood from other less active tissues (e.g., the splanchnic and cutaneous circulations). Thus, O_2 ex-

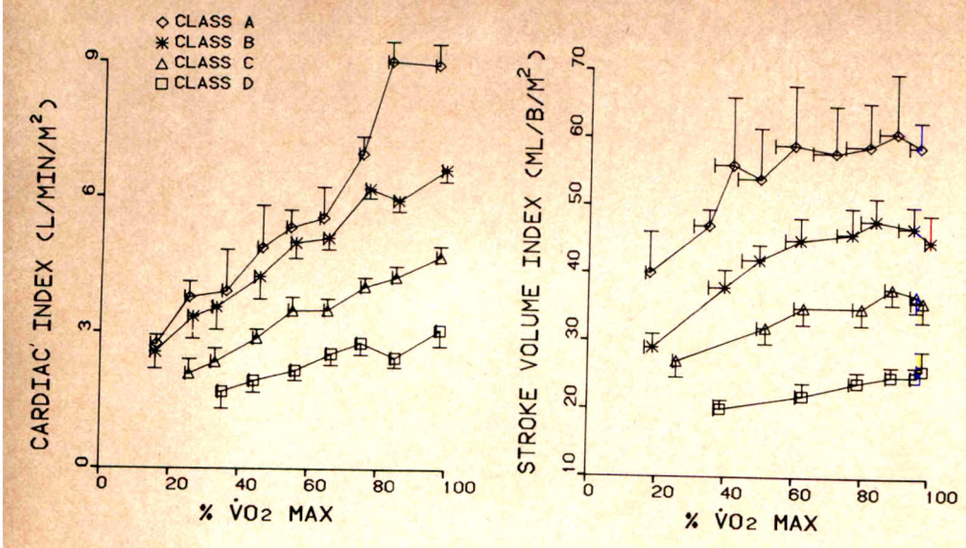


FIGURE 3. Response in cardiac output and stroke volume from standing rest to maximal exercise for each functional class. $\dot{V}O_2$ MAX = maximal oxygen uptake.

traction proceeds to maximal physiologic levels, while the absolute level of blood flow to the exercising limb may be less in patients with CCF.[26] Moreover, the ability of their skeletal muscle circulation to autoregulate may also be impaired.[27]

Given that O_2 extraction by muscle is not impaired, the reduction in aerobic capacity of these patients must therefore be primarily due to the heart's inability to sustain systemic blood flow according to the aerobic requirements of muscle. This is shown in Fig. 3, left, where the response in cardiac output to progressive isotonic exercise is given for each functional class. The resting cardiac output was not significantly different for classes A and B, while it was significantly different for classes B, C and D. At peak exercise the cardiac output was significantly different for each class. Thus, it is the heart's pumping reserve that is primarily responsible for the different aerobic capacities of these patients. Therefore, the $\dot{V}O_2$ max determination is a valuable noninvasive measure of pump reserve and can be used to predict the maximum cardiac output to exercise. Moreover, it can distinguish defects in pump reserve that are not apparent at rest (e.g., between classes A and B).

The cardiac output response to exercise for each class is a function of the heart's ability to raise its stroke

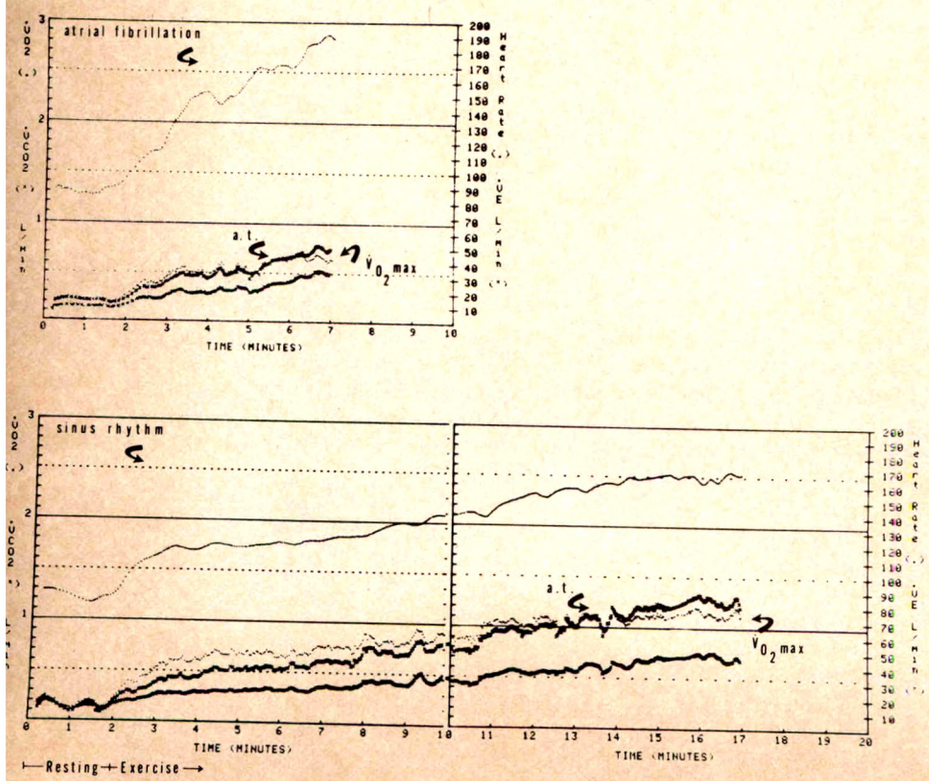


FIGURE 4. Response to isotonic exercise in a 32-year-old woman with mitral stenosis. **Upper tracing,** when the patient had atrial fibrillation and rapid elevation in heart rate during low levels of work, there was significant impairment in aerobic capacity, compatible with functional class D. Note early appearance of anaerobic threshold (a.t.). **Lower tracing,** aerobic capacity was significantly improved to class B, with return to sinus rhythm and more appropriate elevation in heart rate. $\dot{V}O_2$ and $\dot{V}CO_2$ = O_2 uptake and CO_2 production, respectively.

volume and heart rate. In class A and B patients, stroke volume rises during lighter workloads that represent less than 60% of $\dot{V}O_2$ max (Fig. 3); thereafter, stroke volume remains invariant. This response resembles that seen in normal subjects during upright exercise. In class C patients the improvement in stroke volume during the transition from rest to submaximal exercise is modest, whereas in class D, stroke volume does not vary throughout exercise. The most likely explanation for this impairment in stroke volume response is poor myocardial function. In addition, however, as venous return increases during exercise, the pericardium may restrain ventricular filling in these chronically dilated hearts.[28]

In each class the maximal heart rate response to exercise is a function of the maximal workload attained.[5] As a result, maximal heart rate is significantly different for each class. In class D patients, the elevation in heart rate is the sole mechanism by which cardiac output is increased. These observations, which indicate that the increment in heart rate is a function of workload, are contrary to traditional teaching, which suggests that a more dramatic increase in heart rate should occur in class D patients.[29] This latter view, however, is based largely on findings in patients with mitral stenosis and atrial fibrillation. With normal sinus rhythm, this is not the case. Figure 4 illustrates this point in a 32-year-old woman with mitral stenosis. Her exercise response is shown on 2 occasions: when she had atrial fibrillation and a rapid and pronounced increase in heart rate at low workloads, and subsequently after a return to sinus rhythm, where her heart rate response to exercise was in keeping with the expected chronotropic response. At both times, the patient was receiving therapeutic doses of oral digoxin.

In accordance with the Fick theorem, an interrelationship exists among cardiac output, arteriovenous O_2 difference and $\dot{V}O_2$. This relation is shown in Figure 5, where $\dot{V}O_2$ is expressed as isopleths of constant O_2 utilization for a 70-kg person of average body surface area (1.75 m^2), which permits us to convert the traditional expression of cardiac output in liter/min/m^2 to units of $\dot{V}O_2$, or ml/min/kg. From this relation it is apparent that irrespective of the rest cardiac output and arteriovenous O_2 difference, at peak exercise, when maximal O_2 extraction exceeds 70% (corresponding to the arteriovenous O_2 difference represented by the cross-hatched region in Figure 5), the aerobic capacity of the patient will be solely a function of cardiac output. Thus, for class D patients with a $\dot{V}O_2$ max of less than 10 ml/min/kg, maximal cardiac output will be 2 to 4 liters/min/m^2; in classes C, B and A it will be 4 to 6, 6 to 8 and >8 liters/min/m^2, respectively. Once again, the ability of the noninvasive determination of $\dot{V}O_2$ max to predict pump function and cardiac reserve is emphasized.

The response in arterial blood pressure from standing rest to maximal exercise is a function of the increment in cardiac output and the reduction in systemic vascular resistance. Figure 6 shows the response in systolic, mean and diastolic arterial pressures during upright treadmill exercise for each functional class. In class A patients, there is a normal increase in systolic and mean pressures

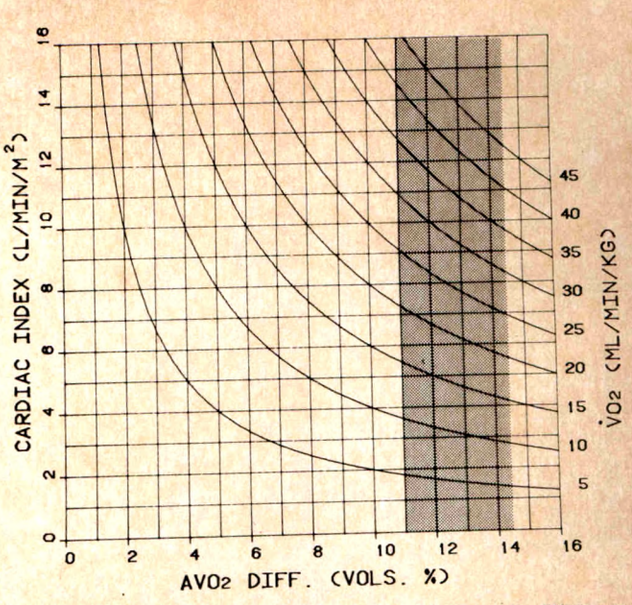


FIGURE 5. Relation among cardiac output, arteriovenous O_2 difference (AVO_2 DIFF) and O_2 uptake ($\dot{V}O_2$). In order to convert blood flow in liters/min/m^2 to ml/min/kg of $\dot{V}O_2$, blood flow data are expressed for a 70-kg person of average body surface area (1.75 m^2). **Cross-hatched area** for AVO_2 difference indicates maximum level of O_2 extraction for commonly observed levels of hemoglobin (i.e., 11 to 14 g/100 ml).

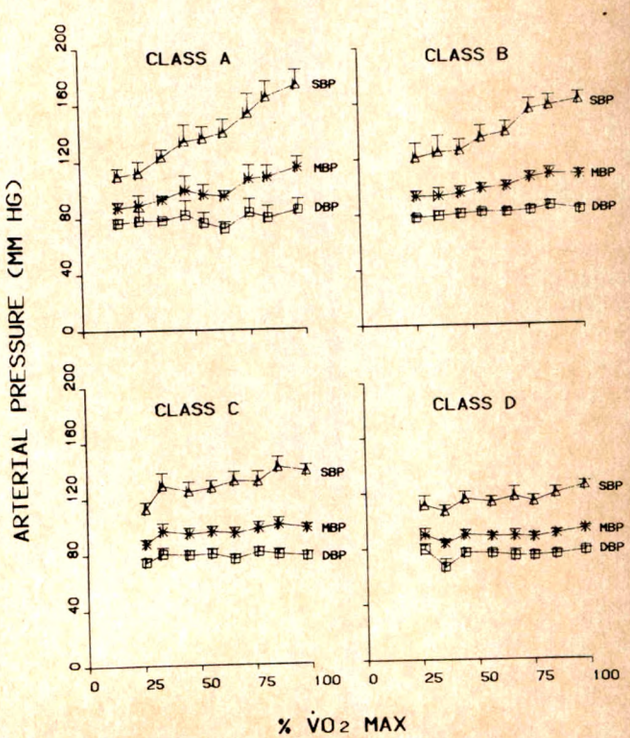


FIGURE 6. Response in arterial pressure (systolic [SBP], mean [MBP] and diastolic [DBP] pressures) for the 4 functional classes and according to level of aerobic work performed. Note attenuation of systolic blood pressure-response to exercise as functional capacity falls from class A to D. $\dot{V}O_2$ = O_2 uptake.

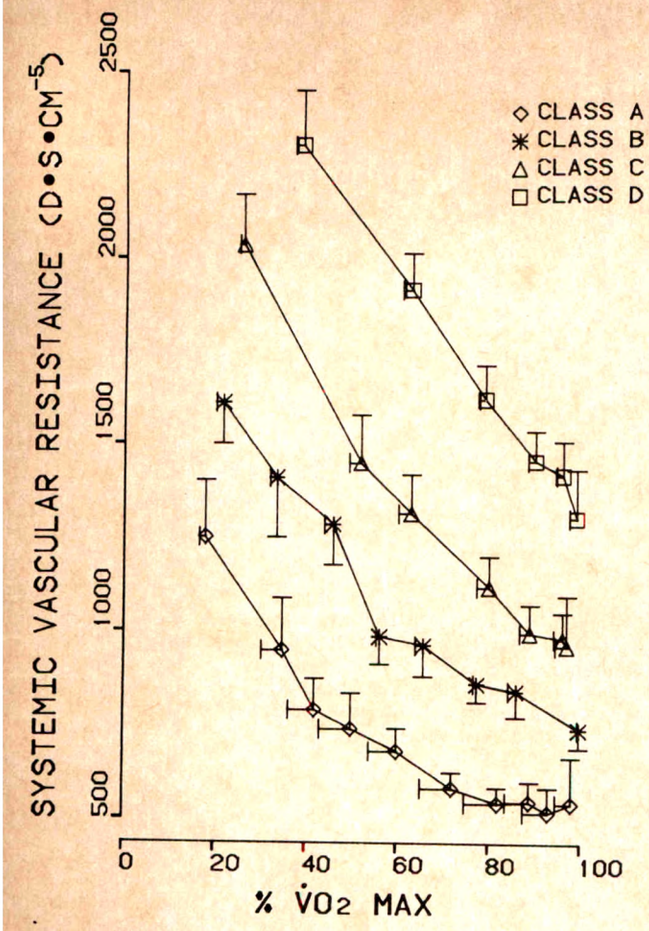


FIGURE 7. Response in calculated systemic vascular resistance from standing rest to maximal exercise for each functional class. In each class there is a progressive decrease in vascular resistance during exercise. $\dot{V}O_2$ MAX = maximal O_2 uptake.

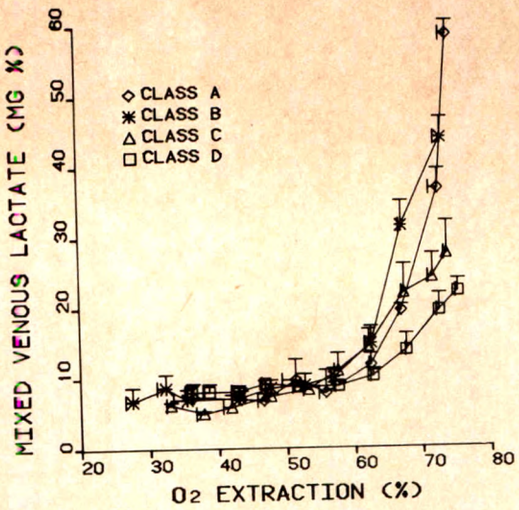
to 176 and 115 mm Hg, respectively, above the rest values (i.e., 115 and 91 mm Hg, respectively) as exercise reaches maximal levels; diastolic pressure remains unchanged throughout exercise, reflecting the progressive vasodilatation of working skeletal muscle. The blood pressure response of class B patients is not significantly different from that of class A patients. In contrast, the increase in systolic pressure is attenuated in class C and D patients. This is particularly evident in class D and is a function of the limited elevation in systemic blood flow in the face of skeletal muscle vasodilatation. None of the class C or D patients experienced lightheadedness or syncope during the exercise test or while recovering in the sitting position.

The decrease in systemic vascular resistance that occurs from standing rest to maximal exercise is shown in Figure 7. At rest, patients with minimal impairment (class A) differed significantly ($p < 0.05$) from patients in classes C and D, in whom a higher vascular resistance was the rule. During exercise, vascular resistance fell approximately 50% in each class. The minimal values of vascular resistance observed at maximum exercise, however, were significantly different ($p < 0.05$) among all but classes A and B. Even though the fall in resistance was similar in each class, the nonlinear relationship between resistance and cross-sectional area of circulation suggests that in patients with advanced CCF the degree of vasodilation of the skeletal muscle may be impaired as Zelis et al[27] have suggested.

Anaerobic threshold: Anaerobic muscle produces lactate. In our laboratory, the normal resting mixed venous lactate concentration is 7 to 8 mg%.[5] We assume that when mixed venous lactate concentration exceeds 12 mg%, which is 3 standard deviations above the average rest value, significant lactate production and release from anaerobic muscle is present. Figure 8, left, depicts the relation between mixed venous lactate concentration and O_2 extraction and the absolute level of $\dot{V}O_2$ attained during treadmill exercise. When systemic O_2 extraction exceeds 60%, lactate production is present. The appearance of anaerobiosis during exercise occurs at 60% or more of the aerobic capacity. Given the difference in aerobic capacity for each functional class, however, different workloads are required for each functional class to reach their anaerobic threshold (Fig. 8, right). In class D patients whose cardiac output response is limited, lactate production occurs at very light workloads requiring only 6 to 7 ml/min/kg of $\dot{V}O_2$ (e.g., 2 mets of work or walking down the corridor at a leisurely pace). In class C, a workload of 9 to 10 ml/min/kg is required before lactate production occurs. In classes B and A, higher loads are tolerated until lactate production occurs (i.e., 12 to 14 ml/min/kg and more than 14 ml/min/kg, respectively). Thus, the onset of anaerobiosis and the corresponding workload, or anaerobic threshold, reflect the severity of chronic cardiac failure. The differences in the absolute increase in mixed venous lactate observed in the classes may be related to differences in systemic and limb blood flow and the corresponding wash-out of lactate from working muscle.

We can noninvasively determine the anaerobic threshold in patients from their response in respiratory gas exchange during incremental treadmill exercise. We use several criteria for this purpose, as noted earlier. During the exercise test itelf, we monitor the temporal response in $\dot{V}O_2$ and $\dot{V}CO_2$ (Fig. 1 and 4), as well as the response in end tidal O_2 (Fig. 9). Consequently, we can immediately determine whether or not the patient has achieved an anaerobic level of work during the test. After the test we further analyze the response in gas exchange according to the criteria stated earlier and also illustrated in Figure 9. Matsumura et al[30] reported their findings regarding the noninvasive determination of anaerobic threshold during treadmill exercise in patients with CCF. Their observations are very similar to ours and support our view that the severity of CCF may be graded according to this measurement.

In summary, the incremental treadmill test, together with the noninvasive monitoring of respiratory gas exchange, heart rate and blood pressure provide two objective criteria, $\dot{V}O_2$ max and anaerobic threshold, by which the severity of CCF can be measured. The test is performed safely and easily by most patients, and is reproducible. If the underlying nature of the heart



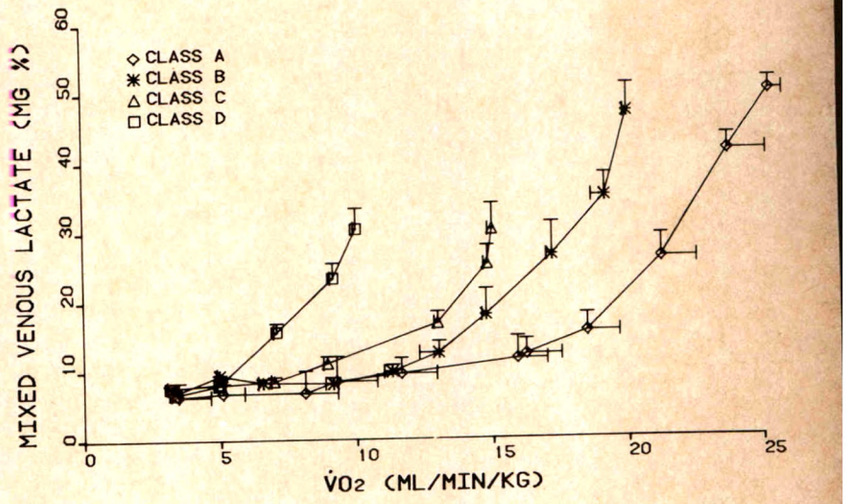


FIGURE 8. Response in mixed venous lactate concentration to exercise expressed as a function of O_2 extraction and level of work, or $\dot{V}O_2$, performed for each functional class. Lactate production (>12 mg%) occurs at different workloads and according to aerobic capacity.

disease is known, no additional testing is required, and the patient's exercise response can be followed serially to determine the natural course of the disease or the response to various therapeutic interventions. We chose this approach to examine the long-term efficacy of various pharmacologic agents in controlled clinical trials.[6–9] Patients receiving placebo in these trials, who were exercised serially over many months, did not alter their $\dot{V}O_2$ max or anaerobic threshold. These observations serve to indicate further the reproducibility of their exercise response.

Differentiating the cause of dyspnea in patients with coexistent heart and lung disease: Exertional dyspnea accompanies a wide variety of disorders, including heart disease, lung disease and pulmonary vascular disease. Many patients with CCF have coexistent obstructive or restrictive lung disease. In these patients it is difficult to identify whether or not the cause of breathlessness is due to heart or lung disease. Exercise testing can be used to elicit dyspnea and together with the measurement of respiratory gas exchange, air flow and ear oximetry aid in differentiating the cause of dyspnea.[8] Our approach is to obtain resting pulmonary function studies first, including measurement of MVV, FVC and peak expiratory flow rate. These data not only identify the ventilatory reserves from which the exercise response is drawn, but also aid in describing the severity of the underlying lung disease. During incremental isotonic exercise, we measure the tidal volume, respiratory rate, $\dot{V}_E$, expiratory flow rate and arterial O_2 saturation by ear oximeter while striving to have the patient reach his anaerobic threshold and $\dot{V}O_2$ max. The maximal tidal volume, maximum $\dot{V}_E$ and maximal flow rate obtained at the symptomatic endpoint to exercise are expressed as a fraction of the FVC, MVV and peak flow rate, respectively. In patients with CCF, and no underlying lung disease, these ratios rarely exceed 50%. Moreover, these patients can attain both their anaerobic threshold and $\dot{V}O_2$ max.[5] In patients with lung disease, in contrast, ventilatory response to exercise utilizes 70% or more of these reserves when the symptomatic endpoint to exercise is reached. Normal subjects also have difficulty sustaining a ventilatory effort above this level.[18,31] Additionally, although pa-

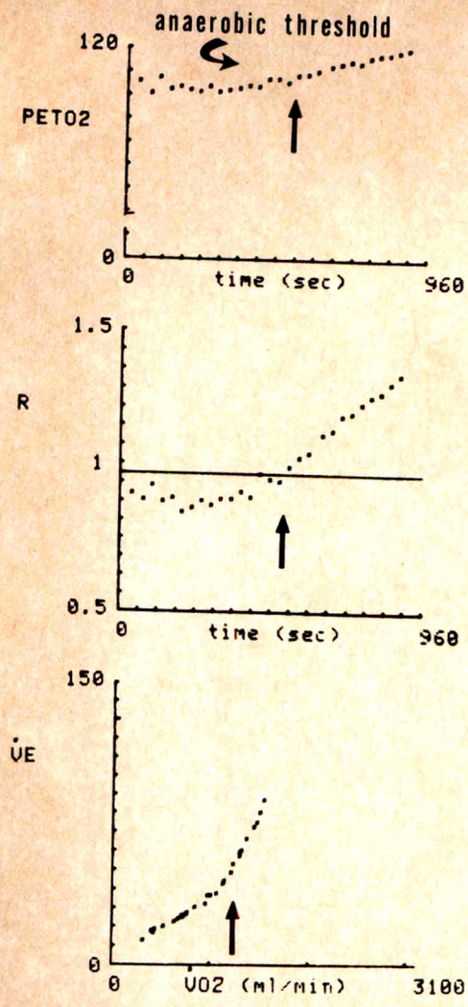


FIGURE 9. Noninvasive determination of anaerobiosis from response in end-tidal O_2 ($PETO_2$), respiratory gas exchange ratio (R) and minute ventilation ($\dot{V}_E$) relative to oxygen uptake ($\dot{V}O_2$) to incremental exercise for patient whose exercise response was given in Figure 1.

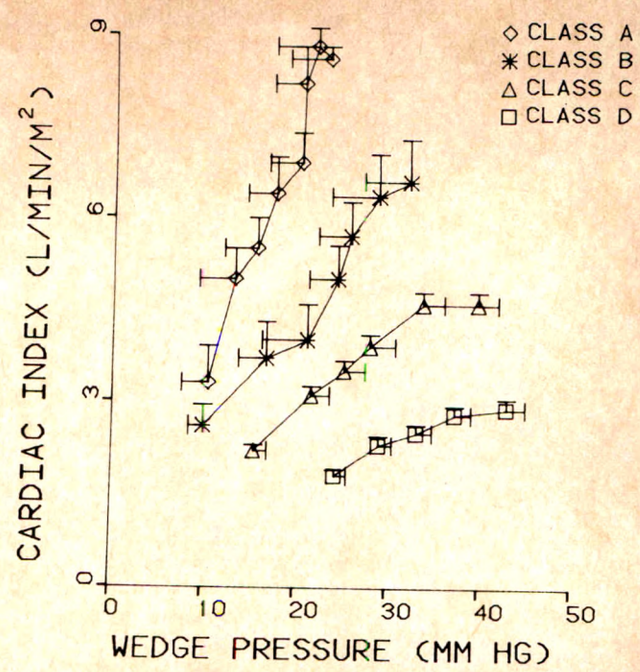


FIGURE 10. Response in ventricular function or elevation in cardiac output compared with left ventricular filling pressure, obtained from occlusive wedge pressure tracing at end expiration, from standing rest to maximal exercise for each functional class.

tients with lung disease may or may not reach their anaerobic threshold when they must stop exercising, they rarely if ever attain their $\dot{V}O_2$ max. Finally, patients with lung disease may demonstrate a fall in arterial O_2 saturation that is not seen in patients with ischemic or cardiomyopathic heart disease. Collectively, these responses aid in distinguishing the cause of exertional dyspnea.

The Invasive Exercise Test in Evaluating the Nature and Severity of Chronic Cardiac Failure

Hemodynamic monitoring: The information that can be obtained by invasive hemodynamic monitoring should be apparent from the foregoing discussion. In patients with CCF, a particular issue of interest is the response in occlusive wedge pressure during exercise. This information can aid in identifying the appearance of mitral regurgitation that is not present at rest. Such a finding may indicate why a patient with apparently adequate resting ventricular function has reduced aerobic capacity. The severity of mitral apparatus dysfunction secondary to a segmental wall motion abnormality or a myopathic process can be demonstrated from the elevation in pulmonary venous pressure that occurs during upright exercise. The relation between exercise cardiac output and and left ventricular filling pressure is given in Figure 10 for our 4 exercise classes. Class C and D patients have marked elevations in pulmonary venous pressure at rest and with any level of exercise, whereas in class B patients elevated wedge pressures develop only during exercise at higher workloads. In class D, the cardiac output response is inadequate despite these levels of filling pressure and indicates the severe impairment in myocardial contractile performance. Despite this pulmonary venous pressure, class C and D patients do not have clinical evidence of pulmonary congestion during or after the exercise test. This may be related to the transient nature of the elevation in pulmonary venous pressure given the limited effort tolerance of these patients, the enhanced lymphatic drainage of their lungs and the alterations in lung tissue pressure.

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Role of Vasodilators in the Treatment of Congestive Heart Failure

T. BARRY LEVINE, MD

Appreciation of the important role played by peripheral vasoconstriction in the pathophysiology of congestive heart failure (CHF) has led to the widespread use of vasodilators as treatment. Short-term studies show that, regardless of the vasodilator used, the arterial and venous dilatation produced invariably results in improvement in the hemodynamic status of patients. This short-term response, however, does not automatically translate to long-term clinical improvement. The reasons for this are not well understood but such factors as differing mechanisms of action, development of tolerance and unique patterns of regional redistribution of blood flow may all play a modifying role in differentiating one vasodilator from another. Nevertheless, a number of controlled trials have demonstrated sustained symptomatic and functional improvment when vasodilators such as the converting enzyme inhibitors or nitrates are given to patients with CHF.

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Vasodilating agents are an accepted part of a comprehensive treatment regimen for patients with congestive heart failure (CHF). Their inclusion represents a realization of the important role played by the peripheral vasculature in the pathophysiology of heart failure.

Traditional therapy consists of administering digitalis to enhance myocardial contractility (thereby "reversing" the primary mechanical dysfunction) and diuretic drugs to rid the body of the excess salt and water build-up that accompany pump failure. While often effective in treating mild CHF, this approach does not consider the deleterious effects that peripheral vasoconstriction plays in further compromising the heart.

As pump function deteriorates and cardiac output decreases, a number of neurohumoral mechanisms (the sympathetic nervous system and renin-angiotensin system) are activated in order to maintain circulatory stability.[1] Arteriolar vasoconstriction results in an increased systemic vascular resistance, and venconstriction causes an increase in both venous return and left ventricular filling pressure. The normal heart, with an adequate reserve, can easily respond to the increase in aortic impedance by maintaining a normal cardiac output, or it can respond to an increase in preload by generating more systolic contractility and increasing stroke volume. Because the failing heart is on a much flatter Frank-Starling curve, increases in preload and afterload add to the heart's workload and further decrease pump function. This in turn activates more neurohumoral vasoconstriction, and thus a vicious cycle is established. Ventricular dysfunction is exacerbated by neurohumoral vasoconstrictor mechanisms and vice versa.

Therefore, the rationale for using vasodilators is to improve the working environment of the heart. Unlike inotropic agents, vasodilators have no direct action on left ventricular contractility, but function by reducing systemic vascular resistance (arteriolar vasodilatation) or left ventricular filling pressure (venodilatation) or both. This short-term hemodynamic effect can be seen in Figure 1, in which sodium nitroprusside was given to 47 patients with severe CHF. Pump function is made more efficient because of a decrease in workload and left ventricular filling. This results in an increase in cardiac output and a decrease in pulmonary pressure. Symptoms associated with either a low flow state or pulmonary congestion are therefore alleviated.

The theoretical appeal of using vasodilators to treat heart failure is reinforced by numerous studies demonstrating the beneficial short-term hemodynamic response to these agents. Yet there are differences among the various agents. Their mechanisms of action differ: some are direct vasodilators, such as sodium nitroprusside, nitrates, hydralazine and minoxidil; some are α_1-adrenergic blockers, such as prazosin and trimazosin;

From the Division of Cardiology, Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

Address for reprints: T. Barry Levine, MD, University of Minnesota Hospitals, Box 79 Mayo Memorial Building, Minneapolis, Minnesota 55455.

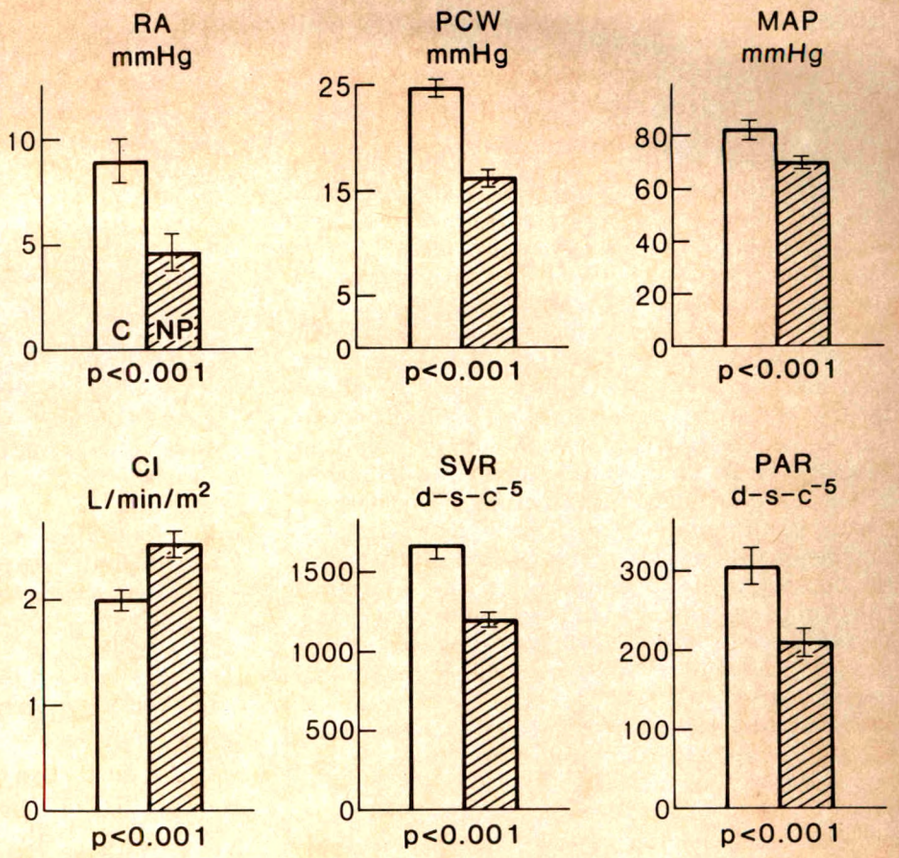

FIGURE 1. Acute hemodynamic response to sodium nitroprusside (NP) in 47 patients with severe congestive heart failure. Effect is balanced with reduction in both resistance and preload. C = control; CI = cardiac index; MAP = mean arterial pressure; PAR = pulmonary arteriolar resistance; PCW = pulmonary artery wedge pressure; RA = right atrial pressure; SVR = systemic vascular resistance.

some are calcium-channel blockers, such as nifedipine; some are angiotensin converting-enzyme inhibitors, such as captopril and enalapril. Furthermore, their sites of action differ. Some have a predominant arterial vasodilator effect such as hydralazine,[2,3] minoxidil[4] and nifedipine[5,6]; some have a predominant venodilator effect, such as nitroglycerin[7,10] and isosorbide dinitrate[11,12]; and some have a balanced venous and arterial effect such, as sodium nitroprusside,[8,13–16] prazosin,[15,16] trimazosin,[17,18] captopril[19–21] and enalapril.[22] Despite these differences, all have been shown to favorably alter the hemodynamic pattern in patients with heart failure. Unfortunately, this short-term hemodynamic response is not a reliable guide to favorable long-term clinical response. The numerous early reports of long-term efficacy must be qualified because the observations were made in open-label trials. Furthermore, several more recent reports indicate that tolerance to these drugs, expecially prazosin[23,24] and hydralazine,[25] does develop.

Can we answer the questions of whether vasodilators are effective long-term therapy and, if so, are some more effective than others? Definitive long-term trials of these drugs are few. Furthermore, studies comparing relative efficacy of one vasodilator with another are only now being undertaken. However, a number of double-blind, placebo-controlled trials have been performed with the most frequently used vasodilators. These studies were similar enough in design to permit comparison. The drugs investigated were captopril,[26] enalapril,[27] isosorbide dinitrate,[28,29] hydralazine[30] and prazosin.[31,32] The patients included were all functionally limited but stable at the time of study. In each of the studies the patients were receiving optional conventional therapy with digitalis and diuretic drugs. Patients were randomized to either active drug or placebo and then monitored for 2 to 6 months with serial clinical evaluations and exercise-tolerance testing. The results of these trials are listed in Table I. Both captopril and

TABLE I Results of Double-Blind Placebo-Controlled Trials Using Vasodilators to Treat Heart Failure

Agent	Mechanism	Clinical Status	Exercise Capacity
Captopril[26] (300 mg/day)	Angiotensin converting enzyme inhibitor	Improved	Increased
Enalapril[27] (5 to 20 mg/day)	Angiotensin converting enzyme inhibitor	Impoved	Increased
Isosorbide[28,29] Dinitrate (160 mg/day)	Direct vasodilator	Improved	Increased
Prazosin[31] (16 mg/day)	α_1 blocker	Improved	Increased
Prazosin[32] (20 mg/day)	α_1 blocker	No change	No change
Hydralazine[30] (200 mg/day)	Direct vasodilator	No change	No change

isosorbide dinitrate improved patients symptomatically and functionally when compared with placebo. On the other hand, neither hydralazine nor prazosin was consistently more effective than placebo in treating patients with heart failure.

It is not clear why captopril and isosorbide dinitrate were effective and hydralazine and prazosin were not. This may be due to a higher incidence of tolerance with long-term hydralazine or prazosin administration even though individual patients did improve. It has been suggested that these drugs stimulate vasoconstrictor mechanisms (sympathetic nervous system or renin-angiotensin system) that override their acute vasodilator activity.[33,34] In the case of isosorbide dinitrate Leier et al[29] demonstrated that long-term efficacy was due to the persistance of venodilator and pulmonary vascular effects even though tolerance developed to systemic arterial dilation. As for captopril and enalapril, their long-term efficacy is probably dependent on a number of physiologic actions. Not only do they block the production of angiotensin II, but they also reduce peripheral sympathetic tone[35,36] and may inhibit degradation of the body's own vasodilator substances, bradykinins,[37] while stimulating prostaglandin production.[38]

These vasodilators redistribute blood flow to regional beds differently. Isosorbide dinitrate increases forearm blood flow but does not change renal or hepatic blood flow.[10,39] Prazosin increases hepatic blood flow.[40] Hydralazine increases both hepatic and renal blood flow to the same order of magnitude as global increases in cardiac output.[39] Finally, captopril and enalapril cause a relative reduction in hepatic blood flow while increasing both renal and cerebral blood flow.[22,41,42] These different patterns of redistribution of regional blood flow may participate in the symptomatic and functional improvement in patients on long-term vasodilators. Further studies are required to confirm this potentially beneficial mechanism and differentiate one vasodilator from another.

Deciding when to initiate therapy with a vasodilator is debatable. Many patients with early CHF will respond adequately to diuretics and digitalis alone. However, even here, the improvement is limited. Exercise testing often reveals significant functional limitation in the otherwise asymptomatic patient.

Certainly patients who remain symptomatic despite aggressive therapy with diuretics and digitalis should be considered for vasodilator therapy. Given the wide range of vasodilators to choose from, selection of a drug for long-term therapy can be tailored to the individual needs and tolerances of the patient. Good data exist for the efficacy of converting enzyme inhibitors such as captopril and enalapril as long-term vasodilator monotherapy. Isosorbide dinitrate also appears to be effective as long-term monotherapy. As a general rule, neither hydralazine nor prazosin seems to be effective, although individual patients may have a good long-term response. The potential benefits of combining different agents working on different vascular beds with different mechanisms of action may be attractive. Hydralazine and nitrates are often used in combination to achieve a balanced reduction of preload and afterload.[43,44] A recent report from Massie et al[45] demonstrated a further improvement in acute hemodynamic response by adding hydralazine to the drug regimen of patients already receiving captopril. This may well be the appropriate solution for the problem of tolerance that is seen with long-term therapy.

We do not know whether the use of vasodilators prolongs the life of a patient with CHF. Symptomatic heart failure carries a poor prognosis, with a 2-year life expectancy of about 50%.[46] By altering the working environment of the heart, vasodilators improve left ventricular function and might delay progression of the disease. The fact that to date no vasodilator has been shown to alter the natural history of CHF may be due to the type of patients studied. As a rule these studies have been performed in patients so severely compromised that they may not have the capacity to reverse a disease process so far advanced. Whether the use of vasodilators in the earlier phases of the disease could alter the natural course of CHF is not known. This rather somber note, however, does not obfuscate the fact that the addition of vasodilator drugs to the standard therapy of digitalis and diuretics may significantly improve the quality of life of patients with CHF.

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Clinical and Hemodynamic Experience with Enalapril in Congestive Heart Failure

ROBERT J. CODY, MD

The renin-angiotension system is activated in many patients with congestive heart failure (CHF), resulting in angiotensin-mediated vasoconstriction and aldosterone-mediated sodium and water retention. To evaluate the effectiveness of enalapril, a new converting enzyme inhibitor, enalapril was administered to patients either orally or intravenously in a single dose, and hemodynamic and hormonal responses were measured. Patients were then placed on oral enalapril therapy for 1 month, and treadmill exercise duration and invasive hemodynamics were compared with baseline pretreatment data. With single-dose administration, both oral and intravenous enalapril reduced systemic vascular resistance and increased cardiac output. However, the effects of oral enalapril were not manifest for 3 to 4 hours, because oral enalapril is a pro-drug form that requires hepatic deesterification. In contrast, intravenous enalapril resulted in significant hemodynamic and hormonal changes 15 to 30 minutes after administration. During long-term therapy, enalapril was associated with improved symptomatology, increase of treadmill exercise duration and sustained hemodynamic improvement. Enalapril was effective therapy for chronic CHF. Optimal short-term response may require coadministration of both intravenous and oral preparations of enalapril; however, the magnitude of the short-term response was comparable for both preparations. Long-term therapy is most effective when the drug is administered as a twice-daily regimen.

(Am J Cardiol 1985;55:36A–40A)

Activation of the renin-angiotensin system in chronic congestive heart failure (CHF) is associated with an adverse hemodynamic profile caused by angiotensin-mediated vasoconstriction and aldosterone-mediated sodium retention.[1,2] Numerous factors may cause the release of renin in CHF[3] and renin is the rate-limiting enzyme for the generation of angiotensin II and aldosterone. Pharmacologic inhibition of the renin-angiotension system activity can occur at several points along the hormonal pathway (Fig. 1). However, the most practical and efficacious blockade of the renin-angiotensin system is by converting enzyme inhibition. This report outlines clinical and hemodynamic observations with enalapril, a long-acting converting enzyme inhibitor, in patients with severe CHF.

From the Department of Medicine, Cardiology Division, The New York Hospital–Cornell University Medical College, New York, New York. This study was supported in part by a General Clinical Research Center Grant (RR-047) from the National Institutes of Health, Bethesda, Maryland.

Address for reprints: Robert J. Cody, MD, Cardiology Division, New York Hospital–Cornell University Medical Center, 525 East 68th Street, New York, New York 10021.

Methods

Eighteen patients with severe chronic CHF were enrolled in this study after providing informed consent for the described procedures. There were 15 men and 3 women aged 41 to 76 years. The cause of CHF was associated with ischemic heart disease in 11 patients and was idiopathic in origin in 8. No patient had valvular heart disease, and all were normotensive, without a history of sustained systemic hypertension. According to the New York Heart Association classification, 4 patients were functional class III and 14 were functional class IV. All patients had been receiving digoxin and diuretic therapy until the time of enrollment in this study, but these agents were withheld on the morning of study. Most patients failed to demonstrate clinical or hemodynamic improvement with other vasodilator drugs, and no vasodilator drugs were administered for at least 3 days before the study began.

Nine patients received oral enalapril (MK-421) as part of a dose-ranging study previously described,[4] and 9 patients underwent short-term dose ranging with intravenous enalapril (enalaprilat, MK-422). After the initial hemodynamic studies were completed, all patients received oral enalapril ranging in dosage from 2.5 to 10 mg administered twice daily. After 1 month of oral therapy, patients were admitted for a repeat hemodynamic study. All hemodynamic studies were per-

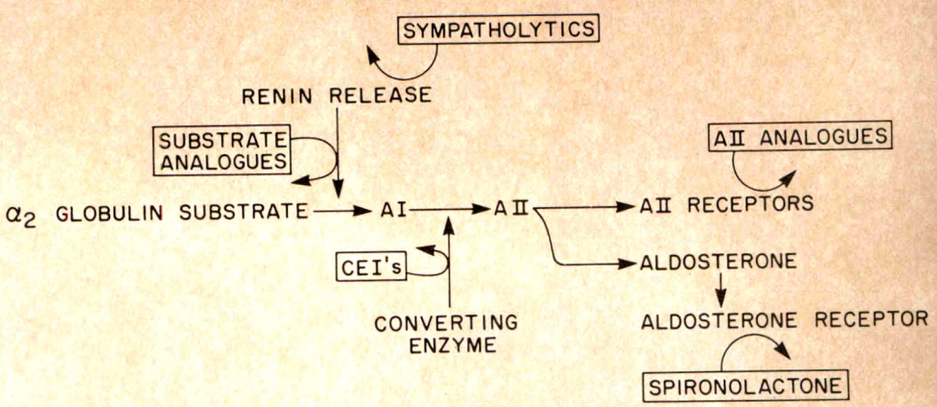

FIGURE 1. Renin-angiotensin cascade and locations for pharmacologic interruption (**enclosed rectangles**). From a clinical and practical point of view, only converting enzyme inhibitors (CEI's) are relevant for therapeutic interventions in congestive heart failure. Figure adapted from Cody and Laragh.[3]

formed the morning after overnight fast, as previously described.[5] Cardiac pressures and cardiac output were measured using a thermodilution right-heart catheter and systemic arterial pressure was determined from an indwelling arterial catheter. The heart rate was determined by continuous monitoring of precordial lead. All patients exercised on a treadmill using a modified Naughton protocol at the time of the baseline and 1-month admission.

Only 14 of the original 18 patients were studied after 1 month of treatment. One patient was lost to follow-up, 1 patient had a sudden cardiac death, 1 patient did not respond to enalapril and was placed on alternate drug therapy and 1 patient had acute renal failure in the setting of enalapril.

Assays of plasma activity and plasma aldosterone were performed using previously described radioimmunoassay techniques.[6,7]

Analysis of variance was used to assess the magnitude of hemodynamic change after the short-term administration of enalapril. To compare the baseline with the 1-month response, a paired t test was used, with each patient serving as his own control. Results were considered statistically significant if they achieved a p value ≤ 0.05.

Results

Table I is a list of the short-term hemodynamic responses to oral enalapril. The baseline hemodynamic values indicate severe CHF: the mean cardiac index was 1.56 liters/min/m^2, mean systemic vascular resistance was 1,687 dyne·s·cm^{-5} and mean pulmonary wedge pressure was 21 mm Hg. After oral enalapril treatment, no significant hemodynamic change was observed for the first 2 hours, with only borderline changes occurring by 3 hours. At 4 hours, however, significant hemodynamic effect was observed, as judged by an increase of cardiac index to 1.81 liters/min/m^2 and a reduction of mean arterial pressure to 67 mm Hg, reduction of pulmonary wedge pressure to 17 mm Hg and a reduction of calculated systemic vascular resistance to 1,378 dyne·s·cm^{-5}. The delay in onset of significant hemodynamic improvement is attributed to the fact that enalapril is administered in a pro-drug form. Enalapril must be metabolized by hepatic deesterification to the active drug, MK-422. This relatively delayed onset of converting enzyme inhibition was confirmed by the time required for appropriate hormonal response. Figure 2 shows the peak response of plasma renin activity and plasma aldosterone. Baseline renin activity was 9 ± 3 ng·ml^{-1}·hr^{-1}, and this increased to 35 ± 11 ng·ml^{-1}·hr^{-1} at 4 hours after oral adminstration of enalapril. Likewise, plasma aldosterone was 19 ± 4 ng/100 ml and this decreased to 9 ± 2 ng/100 ml (for both, $p < 0.02$). However, no significant changes in plasma renin or plasma aldosterone were observed at 1 and 2 hours after oral administration of enalapril.

Because oral enalapril must be metabolized to the active compound, it was difficult to immediately identify the magnitude of hemodynamic response that was likely to occur, as well as the degree of correlation of hemodynamic improvement with baseline renin-angiotensin system activity. For these reasons, we administered intravenous enalaprilat (MK-422), the active converting enzyme inhibitor. When given intravenously, the active compound results in a more dramatic and clear-cut hemodynamic response (Fig. 3). Much smaller doses of the active drug are required to achieve its hemodynamic effect. After an intravenous dose of 0.625 mg, there is prompt and marked reduction of systemic vascular resistance (from 1,998 to 1,497 dyne·s·cm^{-5}), and mean arterial pressure (from 85 to 72 mm Hg), associated with a reflex increase of stroke volume index

TABLE I Acute Response to Oral Enalapril (n = 9)

	Baseline	1 Hour	2 Hours	3 Hours	4 Hours
Heart rate (beats/min)	80 ± 5	81 ± 5	81 ± 6	80 ± 5	77 ± 5
Mean arterial pressure (mm Hg)	74 ± 3	75 ± 4	72 ± 5	68 ± 4*	67 ± 4*
Right atrial pressure (mm Hg)	11 ± 2	12 ± 2	10 ± 2	9 ± 2	9 ± 2
Pulmonary wedge pressure (mm Hg)	21 ± 2	21 ± 2	18 ± 2	17 ± 2	17 ± 2*
Cardiac index (liter/min/m^2)	1.56 ± 0.08	1.69 ± 0.09	1.73 ± 0.11	1.73 ± 0.13	1.81 ± 0.13*
Systemic vascular resistance (d·s/cm^5)	1,687 ± 128	1,552 ± 110	1,520 ± 165	1,459 ± 163	1,378 ± 172*

* $p \leq 0.05$

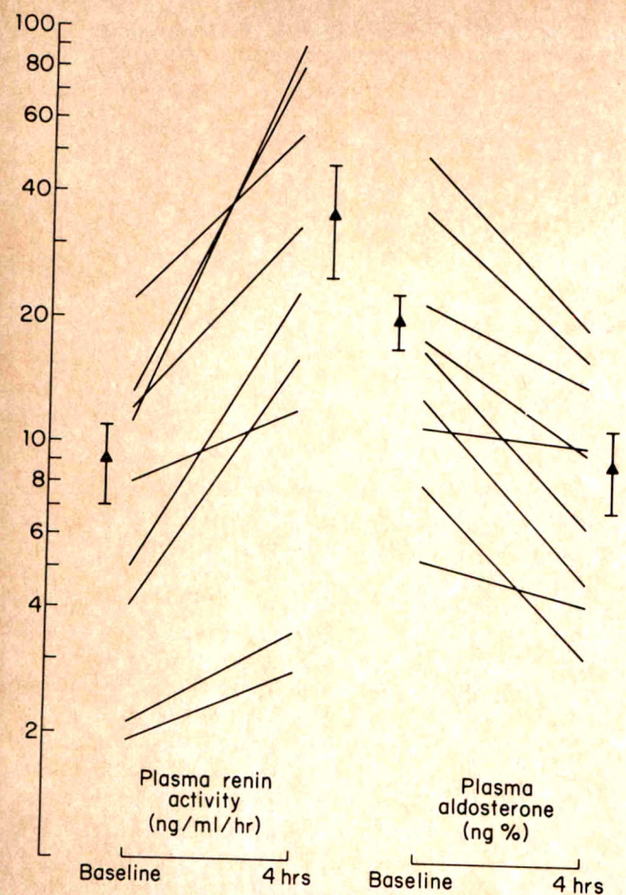

FIGURE 2. Short-term converting enzyme inhibition with oral enalapril resulted in significant increase of plasma renin activity and decrease of plasma aldosterone at 4 hours following oral administration of the drug. Both responses were significant ($p < 0.02$). Reproduced from Cody et al[4] with permission of the publisher.

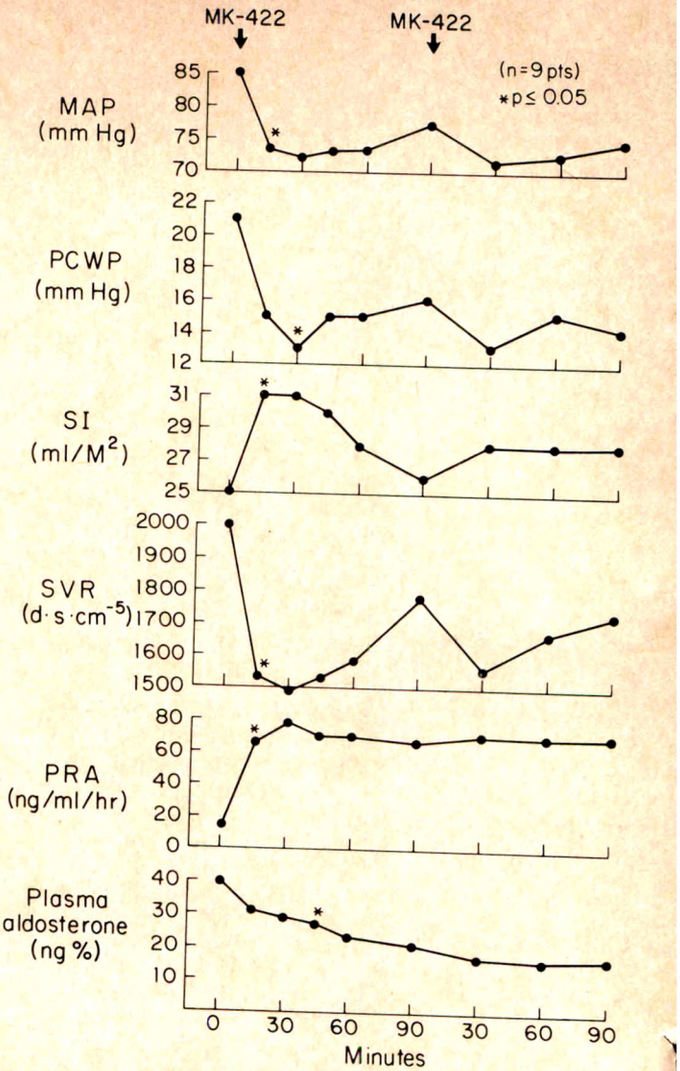

FIGURE 3. Mean hemodynamic and hormonal responses after intravenous administration of 2 doses of MK-422: the first dose was 0.625 mg; the second dose was 1.25 mg. MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; PRA = plasma renin activity; SI = stroke index; SVR = systemic vascular resistance.

(from 25 to 31 ml/m^2) and reduction of pulmonary wedge pressure (from 21 to 13 mm Hg). Within 15 minutes plasma renin activity had increased from 11 ± 4 to 64 ± 7 ng·ml^{-1}·hr^{-1} ($p < 0.001$). Plasma aldosterone changes were slower, owing to the relatively longer circulating half-life of aldosterone. At 90 minutes after administration of the first dose of enalaprilat, attenuation of the hemodynamic response occurred. However, with administration of the second dose, hemodynamic improvement was again observed, although the magnitude of increase of stroke volume index was much less.

To determine whether hemodynamic improvement would be sustained, we repeated the hemodynamic study after 1 month of oral enalapril therapy. We also compared the duration of treadmill exercise at 1 month to that measured at baseline, before drug administration. As shown in Table II, the increase in cardiac index and reduction in mean arterial pressure, pulmonary wedge and systemic vascular resistance were comparable to the observations made at the time of acute hemodynamic study. The plasma renin activity of 27 ± 6 ng·ml^{-1}·hr^{-1} was significantly increased compared with the baseline value of 12 ± 3 ng·ml^{-1}·hr^{-1}, providing evidence of sustained converting enzyme inhibition. This was confirmed by suppression of 24-hour urinary aldosterone excretion at one month. The duration of treadmill exercise nearly doubled from the baseline value of 310 ± 92 seconds to 572 ± 102 seconds.

Objective changes in hemodynamics and exercise duration were accompanied by subjective improvement. The New York Heart Association classification in the baseline state was functional class III for 3 patients and functional class IV for 11 patients. After 1 month of enalapril therapy, the same classification was functional class II for 5 patients, functional class III for 7 patients and functional class IV for 2 patients. In all but the last 2 patients, symptomatology had decreased by at least one functional class. While converting enzyme inhibition may be associated with orthostatic hypotension in the presence of diuretic therapy, this was not the case after one month of enalapril therapy. We were able to

obtain tilt hemodynamics before and after one month of enalapril therapy in 7 patients (Table III). Despite relatively low mean arterial pressure in the supine position, further significant reduction of mean arterial pressure during upright tilt did not occur.

Two adverse reactions were temporally associated with enalapril treatment. In 1 patient, transient acute renal failure occurred within 48 hours of intravenous enalaprilat and oral enalapril administration. This was evident by the presence of oliguria and increases in blood urea nitrogen and serum creatinine levels. When enalapril was discontinued, these values returned to normal levels. The patient declined a renal diagnostic workup to assess the status of his renal arteries. The second adverse reaction was a case of oral mucocutaneous ulceration and evanescent skin rash, which occurred during the fourth week of oral enalapril administration. The mucocutaneous changes resolved 3 to 5 days after discontinuation of enalapril, and the patient was not rechallenged.

Discussion

These data and those reported from others[8,9] indicate that enalapril is effective for long-term symptomatic and hemodynamic improvement in patients with severe CHF. Unlike direct vasodilators, however, the effectiveness of converting enzyme inhibitors depends on their ability to block angiotensin-mediated vasoconstriction. If the circulating levels of angiotension II or angiotensin occupancy of vascular receptors is minimal,[10] converting enzyme inhibitors are not expected to result in significant hemodynamic improvement. Indeed, one patient from our intravenous enalaprilat study had no hemodynamic improvement with enalaprilat and subsequent results from his hormonal profile confirmed suppressed renin-angiotensin activity.

The renin-angiotensin system is not uniformaly activated in CHF[1,2,11] and a number of factors can concurrently stimulate or suppress the extent of renal release. The net effect of these multiple interactions is a potential for fluctuating degrees of angiotensin-mediated vasoconstriction and aldosterone-mediated sodium retention. Some of the factors influencing renin-angiotensin inhibition are listed in Table IV. Probably the most important factor from the clinical point of view is the state of sodium balance, as sodium depletion is

TABLE II One-Month Response to Oral Enalapril (n = 14)

	Baseline		One month
Heart rate (beats/min)	76 ± 5		72 ± 4
Mean arterial pressure (mm Hg)	77 ± 3	*	71 ± 3
Right arterial pressure (mm Hg)	10 ± 1		7 ± 1
Pulmonary wedge pressure (mm Hg)	20 ± 3	*	15 ± 2
Cardiac index (liter/min/m^2)	1.76 ± 0.13	*	2.12 ± .18
Systemic vascular resistance (d·s/cm^5)	1,789 ± 169	*	1,308 ± 132
Plasma renin activity ($ng \cdot ml^{-1} \cdot hr^{-1}$)	12 ± 3	*	27 ± 6
Exercise duration (seconds)	310 ± 92	*	574 ± 102

* $p \leq 0.05$

associated with enhanced renin release.[12,13] In this setting, vascular tone is much more dependent on angiotension II, as compared to normal sodium intake. During sodium depletion, the hemodynamic response to converting enzyme inhibitors such as enalapril is likely to be associated with both supine and postural hypotension. Yet it is in this setting that converting enzyme inhibitors are much more effective for treating patients with CHF. On the other hand, sodium repletion, fluid overload or ineffective diuretic regimens are often associated with suppression of the renin-angiotensin system and endogenous angiotensin II activity;[14] in this setting, converting enzyme inhibitors are less effective. The long-term hemodynamic response to converting inhibitors is usually comparable to the short-term response because sodium depletion and diuretic therapy are generally held constant in heart failure patients. However, one can easily understand that a patient with acute fluid overload may have a poor initial response to enalapril yet respond on a long-term basis when diuretic therapy has been optimized. Conversely, an individual may exhibit a good response to enalapril while in the hospital, but deteriorate on an outpatient basis if dietary sodium is not carefully regulated. Thus, an individual patient's sodium status may be the most important long-term factor in response to converting enzyme inhibition.

In this study, enalapril was associated with simultaneous hemodynamic improvement marked by reversal of vasoconstriction and inhibition of the renin-angio-

TABLE III Effect of Long-Term Enalapril on Postural Hemodynamics

	Control		1 Month		
	Supine	Tilt	Supine		Tilt
Heart rate (beats/min)	81 ± 6	85 ± 5	77 ± 5		82 ± 5
Mean arterial pressure (mm Hg)	72 ± 3	65 ± 1	65 ± 1		63 ± 4
Right atrial pressure (mm Hg)	11 ± 2	4 ± 2	7 ± 2	*	3 ± 2
Pulmonary wedge pressure (mm Hg)	20 ± 3	11 ± 4	17 ± 2	*	12 ± 3
Cardiac index (liter/min/m^2)	1.60 ± 0.14	1.49 ± 0.10	1.81 ± 0.08		1.66 ± 0.07
Systemic vascular resistance (d·s/cm^5)	1,643 ± 203	1,704 ± 183	1,317 ± 60		1,476 ± 90

* $p \leq 0.05$ (comparing supine with tilt)

TABLE IV Factors Influencing the Long-Term Response to Renin-Angiotensin Inhibition

Sodium intake/diuretic therapy
Alterations in renal blood flow and function
Interactions with other hormonal pathways
Progression or abatement of left ventricular dysfunction
Limitations/side-effects of drug therapy

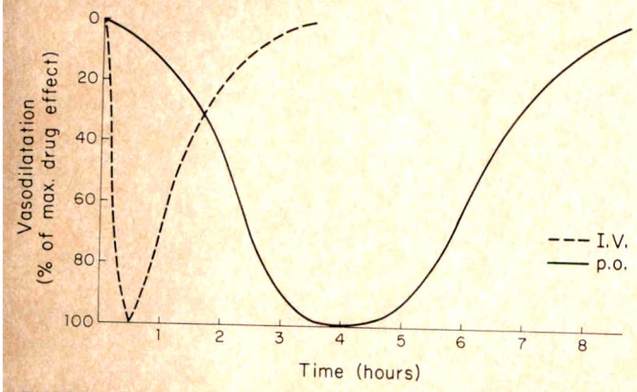

FIGURE 4. Relative time course of action of single dose of intravenous (I.V.) or oral (p.o.) enalapril. Vasodilatation, or reversal of vasoconstriction, expressed as percent of maximal drug effect over time is shown.

tensin system. There was a striking difference in the time course of the short-term response when the oral administration of the pro-drug MK-421, and the biologically active, deesterified active compound MK-422 were compared (Fig. 4). The first dose response must be interpreted in the context of the time course of action of the two different compounds. With intravenous enalaprilat or MK-422, the hemodynamic response to relatively small doses of the drug is prompt, and at times associated with marked reduction of blood pressure. In our experience, if there is no hemodynamic improvement within 60 to 90 minutes following a 2.5-mg dose of intravenous enalaprilat, it is unlikely that angiotensin-mediated vasoconstriction is occurring then, and the patient may require sodium depletion or alternate therapy. On the other hand, a marked response to intravenous enalaprilat suggests enhanced renin-angiotensin system activity and for clinical purposes, it may be necessary to decrease diuretic dosage temporarily. With oral administration of enalapril, the hemodynamic response may not be evident until 3 to 4 hours after its administration. In fact, for individual patients, it may be necessary to wait as long as 6 to 8 hours after drug administration to see a hemodynamic response.[8,9] Optimal oral therapy is 5 or 10 mg twice daily. At the initiation of therapy, it may be reasonable to administer intravenous and oral enalapril in close temporal succession, particularly if urgent intervention is necessary.

In terms of adverse reactions associated with enalapril, we observed one case of acute renal decompensation and one of mucocutaneous reaction.[15] While both adverse reactions were closely associated with the onset of enalapril administration, we cannot directly implicate enalapril in either case because neither patient was subsequently rechallenged with enalapril.

Enalapril has now been studied in more than 30 patients with chronic heart failure (Walker FJ: personal communication). These studies have demonstrated findings similar to those in our own laboratories, but in a broader range of patients. Significant improvement in hemodynamic status as well as exercise tolerance and New York Heart Association functional classification has been observed in patients who responded inadequately to digitalis/diuretic regimens. Patients have been treated with enalapril for periods longer than 2 years; chronic therapy has been well tolerated by most patients.

In summary, enalapril was associated with acute hemodynamic improvement when administered in either an intravenous or oral form. Long-term therapy was associated with improved symptoms and objective evidence of both exercise and hemodynamic improvement. It appears that enalapril is an effective converting enzyme inhibitor for the management of patients with chronic CHF.

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New Positive Inotropic Drugs for the Treatment of Congestive Heart Failure

EDMUND H. SONNENBLICK, MD, DONNA M. MANCINI, MD, and THIERRY H. LeJEMTEL, MD

Positive inotropic agents can stimulate the severely depressed myocardium in late stages of heart failure. However, symptomatic benefits are only gained by improvement in the deranged peripheral circulation, which produces symptoms and limitations. In augmenting cardiac output and reducing filling pressures, the effects of positive inotropic agents and vasodilators are similar and additive, and the "contractile reserve of the heart" in response to inotropic stimulation may limit efficacy of these agents. Although symptomatic benefits occur in patients with severe heart failure after improvement in peripheral blood flow distribution, survival may not be altered, because this appears to be determined more by the amount of myocardial damage and its progression, and neither of these is affected by either inotropic agents or vasodilators. Indeed, in early stages of heart failure, therapy must be redirected toward preventing further myocardial cell loss rather than stimulating pump function.

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Despite optimal current therapy with digitalis glycosides, potent diuretic drugs and vasodilator drugs, patients with severe chronic heart failure remain symptomatic and generally face a progressively declining clinical course with a rapidly fatal outcome.[1] Diuretic drugs are highly effective in control of sodium excretion, while various vasodilator drugs help to reduce the loads the heart must bear. Moreover, digitalis glycosides, which are the only oral inotropic agents clinically available to increase contractile force and, hence, improve depressed ventricular function, are limited in terms of their modest potency and associated toxicity. Thus, the search for new inotropic agents to stimulate the failing myocardium is a major pharmacologic challenge in the treatment of heart failure. At the same time, it is equally important to define the therapeutic target to determine the usefulness of such agents. Failure to do so may result in unfulfilled promises and unrealistic expectations.

The clinical entity of chronic heart failure has 2 components: *myocardial failure*, which leads to both acute and chronic pump dysfunction, and *congestive failure*, a more chronic derangement of the circulation with organ dysfunction resulting from excessive compensatory peripheral vasoconstriction and redistribution of peripheral blood flow. Myocardial failure can occur from a sustained overload with severe primary ventricular hypertrophy or from loss of myocardium, either segmental, as in coronary artery disease, or diffuse with focal loss of myocardium, fibrosis and resultant secondary hypertrophy, as in cardiomyopathies.[2,3] Hypertrophy of severe degree is then associated with depressed myocardial function, possibly because of abnormal calcium activation and decreased contractile protein function.[4] With substantial myocardial depression, ventricular dysfunction occurs; it is characterized by reduced systolic emptying despite increased diastolic volume, which translates clinically into a reduced ejection fraction and limited increase in cardiac output associated with effort.

The second component of chronic heart failure is congestive heart failure (CHF), which is the response of the circulation to pump dysfunction resulting from myocardial failure. Both the sympathetic nervous system and renin-angiotensin system are activated in CHF and contribute substantially to these vasoconstrictive changes.[5,6] Clinically, exertional fatigue results from a limited cardiac output, and shortness of breath and edema result from central and peripheral congestion. Sodium accumulation is also accompanied by profound alteration in peripheral blood flow distribution. Arterial vascular resistance is increased; in particular, it does not decrease normally during exercise so that blood flow to skeletal muscle is limited.[7,8] As will be discussed further,

From the Division of Cardiology, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York.

Address for reprints: Edmund H. Sonnenblick, MD, Department of Medicine, The Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461.

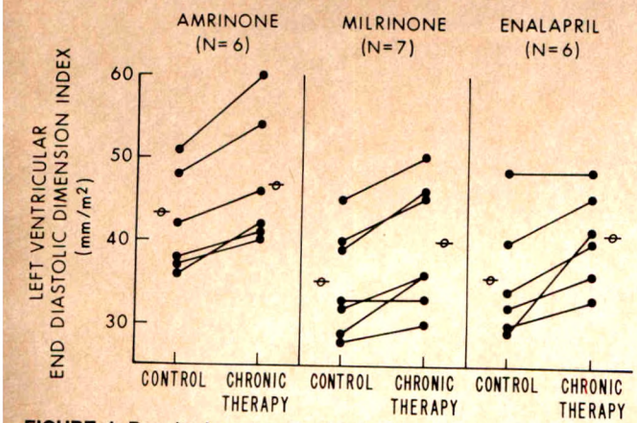

FIGURE 1. Despite long-term inotropic therapy with amrinone for a mean duration of 41 weeks (range 30 to 72) and milrinone for a mean duration of 50 weeks (range 30 to 79), or vasodilator therapy with an angiotensin converting enzyme inhibitor, enalapril, for a mean duration of 57 weeks (range 34 to 66), underlying myocardial disease progresses, as evidenced by increase in left ventricular end-diastolic dimension index (LeJemtel et al: unpublished observations).

limitation of function and changes in clinical status commonly reflect alterations in peripheral blood flow distribution rather than changes in ventricular contractility. Indeed, the ejection fraction, which reflects the extent of myocardial failure, correlates poorly with exercise performance,[9] although it correlates well with survival.[10] In acute heart failure, central fluid accumulation with limited cardiac output is a predominant feature and the peripheral derangements of CHF are generally absent.

The aim of treatment is essentially 2-fold: amelioration of symptoms and prolonged survival. These are not synonymous and need to be considered relative to the nature, severity and stage of disease. Most of the clinical trials in heart failure focused, quite naturally, on severe failure (class III and IV) with the aim of relieving symptoms. The effectivness of treatment was generally measured in terms of exercise performance. The assumption was that an increase in ventricular performance, characterized by an increase in cardiac output and a decrease in venticular filling pressure, would improve delivery of blood flow to exercising muscle and, hence, permit increased exercise performance. However, this has not been the widespread experience. Vasodilators such as captopril produce an immediate increase in caridac output, but exercise performance is not augmented until a few weeks have passed.[11] This reflects the fact that the immediate increments in cardiac output are distributed to the kidneys rather than exercising muscle.[12,13] Dobutamine, a potent inotropic agent, also augments cardiac output substantially while reducing filling pressure, but again blood flow to exercising muscle is not increased, so that exercise performance is not augmented immediately and arteriovenous oxygen difference actually narrows.[14]

In severe CHF, increased peripheral arterial resistance is not fully understood, but may reflect increased renin-angiotensin activity, increased α-receptor stimulation resulting from increased circulating norepinephrine or local mechanical changes in peripheral arterioles, perhaps secondary to sodium and water accumulation. Exercise performance is coupled to these limitations of skeletal muscle flow and as noted, either inotropic agents such as milrinone or vasodilators such as captopril, which exert similar and indeed additive hemodynamic effects,[15] do not increase exercise performance immediately. Thus, merely increasing ejection fraction and cardiac output may not improve symptoms because a substantial period is required before peripheral blood flow distribution improves, especially to exercising muscles. While changes in ventricular performance are very rapid in onset, changes in periphery circulation are not, so that either improvement or deterioration of the patient requires time and does not parallel the rapid improvement in cardiac function.[16] Some recently developed inotropic agents with direct arteriolar vasodilating properties, such as amrinone and milrinone,[17,18] can produce immediate dilatation of the skeletal muscle vasculature and rapidly increase submaximal exercise performance.[19]

The dismal survival rate of patients with severe heart failure is now well recognized[1] and has not been shown to be influenced by either vasodilator or inotropic therapy. This is not surprising if the pathologic characteristics of severe chronic heart failure are considered. Whereas ejection fraction, which reflects the extent of ventricular damage, does not correlate with exercise performance, it does predict survival.[9] Moreover, while chronic drug therapy may improve blood distribution and thus result in symptomatic improvement, the underlying cardiac disease appears to progress and ultimately leads to the death of the patient.[20]

Whether the inotropic agent itself contributes to further myocardial deterioration is not clear.[21] However, we have observed a progressive left venricular dilatation after long-term administration of both vasodilators and inotropic agents (Fig. 1). The fact that both types of agents produce the same end result despite fundamentally different modes of action suggest that "overstimulation" of the heart from the inotropic agent is not in itself producing further damage. It is of interest that the myocardial oxygen requirements of the heart actually decline when the depressed heart is reduced in size by inotropic agents. This decrease in oxygen use correlates with decreases in systolic wall stress, which far outweigh any increase in oxygen need that an augmented contractility might produce.[22] However, inotropic agents in general can induce ventricular arrhythmias and thus may contribute to the high incidence of sudden death in patients with severe heart failure. This possibility requires further study.

With these considerations in mind, the aims of treatment must be established in severe, as opposed to mild, heart failure. In severe failure, symptomatic relief is the primary endpoint, given the extensive cardiac damage that is generally present. "Cure" of the pathologic process is not possible, except with heart transplantation. Symptomatic relief is predicated on increasing the reduced cardiac output, although increments in skeletal muscle flow are necessary if exercise performance is to be enhanced.[23]

In contrast, the major therapeutic aim in the treat-

ment of patients with mild heart failure is preservation of myocardium rather than relief of symptoms.[24] Cardiac output is geneally normal at rest, and with exercise it increases substantially so that exercise performance may only be limited moderately, if at all. Prevention of sodium accumulation with diuretics may be all the treatment required. Inotropic stimulation of the heart to augment cardiac output may not be indicated because output is already normal. Indeed, such inotropic stimulation may actually be contraindicated, especially if calcium overloads may be a potential cause of small vessel disease and myocardial cell death.[25] The major aim at earlier stages of failure is to protect and preserve myocardial tissue and thus hopefully affect long-term prognosis. Whether early use of vasodilators to reduce loads and maintain smaller ventricular volumes will alter progression as well requires definitive study. Verapamil has been used in experimental cardiomyopathies[26] to stabilize cell membranes, inhibit small vessel spasm and prevent cell death; applicability of such experimental observations to man is not known.

In acute severe heart failure, acute pulmonary edema generally reflects acute abnormalities of ventricular function, yet chronic maldistribution of peripheral blood flow may not have occurred. Combined therapy with vasodilators, including morphine, potent, intravenously active cardiac stimulants such as dobutamine,[26] and diuretic drugs combine to produce immediate benefits when the underlying myocardial problem is reversible or limited.

In the normal as well as in the failing heart, cardiac muscle is only partially activated, and the extent of activation depends on the amount of calcium made available to the contractile system with each beat. The final common pathway of all inotropic agents appears to be the enhancement of calcium made available to activate the myocardial cell. Inotropic agents do not correct specific abnormalities in either the contractile apparatus or its activating system. The assumption with heart failure is that despite decreased overall ventricular function, the myocardium is still not fully activated, i.e.,there is a "contractile reserve" (Fig. 2). This may not be so in all cases and when myocardial failure is severe, little or no further ability to stimulate the myocardium may remain. Moreover, with drugs that are both inotropic agents and vasodilators, the primary action to improve cardiac performance, i.e., increasing cardiac output and decreasing ventricular filling pressure, may differ from case to case depending on whether significant myocardial contractile reserve is present.

Digitalis glycosides, which inhibit membrane Na+K+ ATPase to increase intracellular calcium, are modestly potent inotropic drugs. Their therapeutic use is limited by a lower toxic:therapeutic ratio. Catecholamines, which are depleted from the myocardium in severe failure, can still stimulate β_1 receptors in the failing heart. In severe failure, the density of β_1 receptors in the myocardium is reduced, which may make the heart less responsive to the inotropic effects of catecholamines.[27] Alternatively, the effective sympathetic nerve denervation seen in heart failure could enhance the availability of cathecholamines to the receptor sites (supersensitivity). The relative role of these opposing effects are unknown. Intravenous dopamine increases cardiac output and lowers filling pressure at rest, but these effects are lost during exercise, presumably owing to the increased endogenous circulating catecholamines that may saturate available myocardial receptors.[28] Dopamine is a less potent cardiotonic agent than dobutamine, but it specifically increases renal blood flow by stimulating dilatory dopaminergic receptors.[29] Levodopa, which is an orally active precursor, may be a useful adjunct in therapy if it is tolerated.[30]

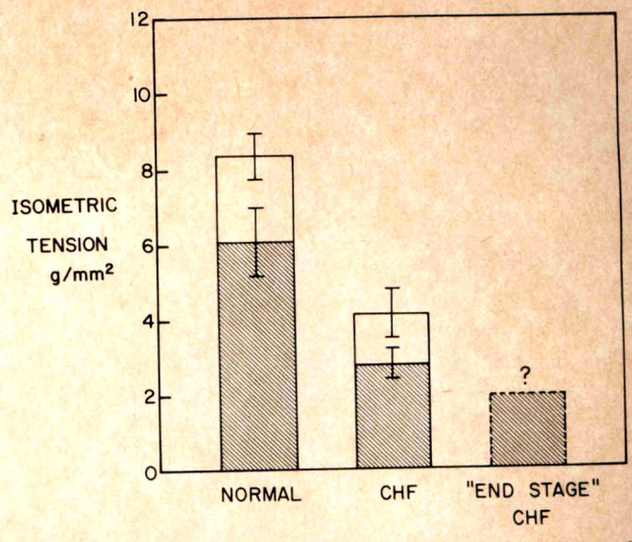

FIGURE 2. Effects of strophanthidin on maximal isometric force of contraction at length of muscle corresponding to apex of the active length-tension curve in 2 groups of muscles. To the right, hypothetical representation of muscle in presence of "end stage" heart failure (CHF). **Hatched area** of each **bar** represents average control force; **clear area** represents average maximal isometric tension achieved following strophanthidin; **vertical lines** with **cross bars** indicate 1 standard error of the mean. Adapted from Spann et al, Circ Res 1967;21:348.

A new class of agents has been developed that are neither catecholamines nor digitalis glycosides. Amrinone was the first agent to undergo clinical trials. It produces phosphodiesterase inhibition and exerts both positive inotropic action and periphexal arterial dilatation.[31] Milrinone is an analog of amrinone and is 30 to 50 times more potent. Its hemodynamic benefits are similar to those produced by amrinone, but its long-term administration has not been complicated by the side effects observed with oral amrinone.[16,18] All of these agents have a similar effect on left ventricular performance, although the relative amounts of inotropic and dilating activity may differ. They were mostly studied in class III and IV patients, and shown to increase cardiac output and reduce ventricular filling pressures without significantly altering heart rate or blood pressure. Hemodynamic benefits were consistently observed and summate with those of vasodilators.[32] Combined vasodilator and inotropic therapy also provides for optimal blood flow distribution, such as increasing renal blood flow as well as reducing aldosterone secretion, as seen with captopril, and augmenting skeletal muscle blood flow and hence, exercise performance, as seen with milrinone.[15]

Although amrinone and milrinone both increase output and reduce filling pressure, the relative contributions of positive inotropic action and direct peripheral arterial vasodilation in producing these changes may vary from patient to patient. While routine hemodynamic measurements of cardiac output and ventricular filling pressures are affected similarly and in an additive manner by both actions, increments in the rate of left ventricular filling pressure development or increase in systolic emtyping of the ventricle for the same pressure are only produced by positive inotropic action. These latter effects are variable with the use of amrinone even when the hemodynamic measurements of output and filling pressures are improved. Nevertheless, although variable, the positive inotropic action apparently prevents systemic hypotension, which occasionally complicates the administration of pure peripheral vasodilators. Relative to inotropic and vasodilator effects, the dose-response curves for positive inotropic action and peripheral vascular smooth muscle relaxation may be different. Thus, at low doses, milrinone causes increments in cardiac contractility that tend to level off as the dose increases, while substantial vasodilation occurs with large doses of the agent.[33]

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Potential for Altering the Natural History of Congestive Heart Failure: Need for Large Clinical Trials

CURT D. FURBERG, MD, SALIM YUSUF, MRCP, DPhil, and THOMAS J. THOM

Congestive heart failure (CHF) is a major clinical and public health problem; moreover, its incidence is increasing. Once this syndrome is manifest, the mortality rate is very high. To date, none of the drugs available for its treatment has been shown to reduce mortality. It is theoretically possible that in patients with overt CHF, drug treatment may not alter prognosis. This hypothesis suggests that patients at high risk of heart failure should be treated before CHF becomes manifest. Alternatively, the trials of patients with manifest CHF may have been unpromising, simply because they were too small. These considerations indicate an urgent need for very large studies of both categories of patients—a "prevention" trial in those without overt CHF and a "treatment" trial in those with overt CHF.

(Am J Cardiol 1985;55:45A–47A)

Congestive heart failure (CHF) is not a disease per se, but a common clinical manifestation of many different heart diseases in which there is extensive myocardial damage or poor left ventricular function. The 2 most common causes of this syndrome are atherosclerotic heart disease and hypertension, each of which contributes to about one-third of all cases. It is estimated that 2.3 million Americans suffer from CHF and approximately 400,000 new cases are diagnosed every year.[1] Because the prevalence of CHF increases with age and because patients with various cardiac diseases live longer owing to advances in medical and surgical management, the number of patients who develop CHF is expected to increase in the next few decades. This increase is already apparent. For example, the National Center for Health Statistics estimates that the number of hospital discharges for CHF (first listed and secondary diagnoses) almost tripled between 1970 and 1982 from 570,000 to 1,557,000.* In this report we discuss what is needed to reliably study the effect of drugs in reducing mortality in patients with CHF.

Effect of treatment on survival: Digitalis and diuretics are the mainstay of treatment for patients with CHF. Although these drugs were never shown to improve survival, they undoubtedly are effective in relieving some of the symptoms. Indeed, many cardiologists view these agents as indispensable; thus the sort of studies required to evaluate their effects on survival may never be undertaken. Because the information on digitalis and its effect on mortality is inadequate, the efficacy and safety of digitalis are under a cloud,[2] despite its use in several millions of patients over two centuries.

There have been several trials of other agents. Furberg and Yusuf[3] reviewed data from all available placebo-controlled trials of long-term vasodilator treatment in patients with CHF to evaluate whether these drugs can improve survival. We identified 18 published or unpublished randomized studies in which various vasodilators—α-adrenergic blockers, isosorbide dinitrate, hydralazine, minoxidil and angiotension converting enzyme inhibitors—were evaluated. All the trials were far too small to detect even large reductions in mortality and in only 1 study were patients treated for longer than 6 months. The largest trial enrolled only 106 patients. Most trials included patients who were functionally in New York Heart Association classes II to IV. The combined data from the trials of angiotensin converting enzyme inhibitors (captopril and enalapril) appear particularly promising and suggest that large long-term trials of this type of agent are justified. Thus, it appears timely to undertake trials of sufficient scope to determine whether treatment of CHF improves survival. We focus on the main considerations that go into the planning of such trials.

Selection of the study population: The incidence of CHF is highly age-dependent. Unpublished data from the National Center for Health Statistics' hospital

From the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Maryland.

Address for reprints: Curt D. Furberg, MD, Acting Associate Director, CAPP/DECA, National Heart, Lung, and Blood Institute, Federal Building, Room 216, Bethesda, Maryland 20205.

* Unpublished data from the Hospital Discharge Survey 1982, National Center for Health Statistics.

TABLE I **Rate of Hospitalization for Congestive Heart Failure* as the First-Listed Discharge Diagnosis by Age and Sex in the U.S. (Rate per 10,000 Population) in 1970–1972 and 1979–1981**

	Men			Women		
Age	45–64	65–74	75+	45–64	65–74	75+
1970–1972	11.9	47.6	115.8	7.7	36.8	85.1
1979–1981	16.7	84.0	220.8	13.1	65.8	196.9

* ICD/8 code 427.1 and ICD/9 code 428.
Source: Unpublished estimates from the Hospital Discharge Survey, National Center for Health Statistics.

discharge survey (Table I) show that for both men and women, hospitalization rates are about 10-fold higher for those aged 75 years or over compared to the youngest group aged 45 to 64. Thus, the criterion for age eligibility in a trial will substantially influence potential recruitment, and enrollment of patients up to the age of 80 years should be considered. Further, any trial ought to consider both men and women for enrollment, as patients of either sex demonstrate a substantial incidence of CHF.

It is also important to consider the optimal time for initiation of treatment. The general experience from prevention trials in the cardiovascular field indicates that early intervention is more successful than late intervention. This is illustrated by some results from the Hypertension Detection and Follow-Up Program.[4] Referred-care participants with diastolic blood pressure between 90 and 104 mm Hg and end organ manifestations (history of myocardial infarction, stroke, intermittent claudication, left ventricular hypertrophy or creatinine levels 1.7 mg/dl) had a 5-year mortality rate of 17.8%, or more than 3 times that of participants with no such manifestation (5.6%). However, stepped-care therapy in this diastolic blood pressure stratum reduced the mortality rate by 27% in the group without end organ manifestations, compared to a reduction of approximately 7% in the group with such manifestations.

Types of trials: In principle, 2 kinds of trials can be conceived: prevention trials and treatment trials. A prevention trial enrolls patients free of overt CHF but at high risk for subsequent development of CHF. An advantage of such a trial in patients with no or only mild symptoms of CHF is that it could have a placebo group. A treatment trial, by contrast, enrolls patients who already are symptomatic. In such a trial, patients with various underlying pathologic conditions (hypertension, coronary artery disease or cardiomyopathy) are included. Randomization could be stratified within each of these groups to assess if even in advanced heart failure, etiology determines whether a treatment is beneficial or not. To this end, heterogeneity in patient selection is very useful. Such a trial would, by necessity, be based on a comparison of active treatments or a placebo-controlled study of an agent added to standard therapy. Both the prevention and treatment trials would have all-cause mortality as the outcome of primary interest.

Sample size considerations: In order to gauge sample size for a trial, 3 important considerations should be addressed: (1) What is the likely mortality rate in the control group? (2) What is the likely benefit? Or more appropriately, what is the smallest benefit that should not be missed? (3) What is the compliance likely to be?

To predict what the control-group mortality rate is likely to be, one should review data from previous observation studies and from other trials (if there are any). The mortality rate observed in these studies is then generally used as the expected control-group mortality rate. However, using this approach, the actual mortality rate in most large scale trials has been about 20 to 40% lower than expected (Yusuf and Friedman, unpublished observations). When this occurs, the "power" of a study is substantially reduced. This lower than expected mortality rate is due in part to the restricted inclusion of only "eligible" patients, and in part because some of the highest risk patients are electively treated and therefore excluded. Thus, we prefer to moderate our expectations of whatever mortality rate is suggested by previous studies. For example, if a 30 to 35% mortality rate is observed in particular types of patients in a study, our expectations in a trial would be about 20 to 25%. In the Coronary Artery Surgery Study, patients with an ejection fraction of less than 0.35 had a 3-year mortality rate of 45% if they were symptomatic and 22% if asymptomatic. Therefore, one would predict that in a prevention trial of asymptomatic patients with an ejection fraction less than 0.35, the mortality rate at 3 years would be 16 to 18%, and in a treatment trial of symptomatic patients with the same ejection fraction, the mortality rate would be about 30% over 3 years.

Estimating what treatment benefits are likely to be observed in a trial is even more hazardous, even when pilot studies exist. Only moderate benefits have been observed in mortality rates with most cardiovascular treatments, including surgery.[5] Thus, experience does not lead us to expect big effects, e.g., 40 to 50%, but instead more moderate reductions, 20 to 25%, in mortality rates. If these estimates appear unduly pessimistic, it should be noted that widespread use of a drug that reduces the risk of death in patients with CHF by about 20% would save 30,000 to 40,000 lives per year in the U.S. alone. Further, any trial that produces convincing evidence before the end of the planned follow-up period because of unexpectedly greater benefit can always be terminated ahead of schedule.

As in most trials of prolonged treatment, one would expect about 20 to 30% of patients to discontinue active treatment because of side effects or other reasons, and about the same number of patients initially assigned to control to start the active agent over the 3 to 4 years of the trial. This has the effect of further reducing any observed benefit.

These considerations suggest that about 4,000 patients are required for a 2-armed prevention trial and about half this number for a treatment trial. Because this combined number appears formidable and is about 10 to 20 times larger than any study of CHF completed thus far, the design of the main study would have to be

TABLE II Instantaneous and Noninstantaneous 25-Month Mortality Rates (%) by Risk Group and Treatment in the β-Blocker Heart Attack Trial

Complication	Propranolol	Placebo	Relative difference (%)
	Instantaneous Death		
None	1.7	1.9	12
Electrical only	2.5	5.0	50
Mechanical	3.1	6.0	49
	Noninstantaneous Death		
None	4.5	4.6	5
Electrical only	2.7	5.9	54
Mechanical	8.7	11.0	21

streamlined to make it practicable. Such a study could still provide information on questions other than mortality by incorporating detailed investigations in some subsets of patients.

Selection of intervention: It seems reasonable to propose testing a single drug—a vasodilator or perhaps an inotropic agent—in a prevention trial in coronary patients free of symptoms of CHF but with a low ejection fraction. On the other hand, in a treatment trial a combination of drugs or a "step-up" treatment schedule seems advisable. Past efforts to test single drugs in survival trials of patients with advanced coronary disease were generally not rewarding. An intriguing possibility is to combine the treatment of CHF with an antiarrhythmic agent, since it is known that almost half of the patients with overt heart failure die suddenly. Recent data from the Beta-Blocker Heart Attack Trial lend support to the idea of combination therapy (Table II). In this study, treatment with β blockers substantially reduced sudden death in patients with moderate left ventricular dysfunction (mechanical failure), presumably through an antiarrhythmic mechanism.[6] Alternatively, combining an inotropic agent with a vasodilator may be beneficial. If the question of combination therapy is to be actively pursued, a factorial design may be appropriate for assessing the effect of each component.

In summary, randomized controlled trials on the effect of drug treatment on survival in patients with CHF are feasible using a collaborative approach. Such trials are necessary before the use of the newer vasodilators and inotropic agents, which appear promising, becomes widespread. Two kinds of trials should be considered: first, a placebo-controlled trial of high-risk patients with no manifestations of CHF, in an attempt to prevent progression to overt heart failure and death (prevention trial); second, a trial of patients with overt CHF, to evaluate the effect of a new vasodilator or inotropic agent over and above standard therapy on mortality (treatment trial). To have reasonable power of detecting important differences, these studies should include about 4,000 asymptomatic and about 2,000 symptomatic patients. To be practicable, a relatively streamlined protocol is required. Other questions besides mortality could be assessed reasonably in smaller subsamples of the study patients.

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Calcium-Channel Blockers: Present Status and Future Directions

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Calcium-Channel Blockers: Present Status and Future Directions

Introduction

STEPHEN E. EPSTEIN, MD, DOUGLAS R. ROSING, MD, and C. RICHARD CONTI, MD

Since the original description by Fleckenstein in 1967 of an agent that manifested effects on conduction tissue apparently compatible with "calcium antagonist" actions, a veritable explosion of investigations has taken place. The calcium antagonists—or, as more currently referred to, the calcium-channel blocking agents—have been used as molecular probes to determine both the basic physiologic and pathophysiologic workings of tissues and organs, and as clinical agents to treat a wide variety of diseases.

This symposium was conceived so that experts in the basic and practical applications of calcium-channel blocking agents could be brought together to discuss the many aspects of this very complex field. The 28 articles in this symposium represent the fruit of that conference, which took place November 17 to 19, 1983. The symposium includes reports that deal with the basic cellular mechanisms responsible for the actions of calcium-channel blockers, including the effects of inhibiting calcium fluxes on excitatory and conducting tissues, on smooth muscle cells of blood vessels and of the gastrointestinal tract and on platelet function. The basic mechanisms modulated by calcium fluxes are also discussed in the context of diverse disorders that often are, or may be, responsive to the calcium-channel blockers, such as angina pectoris, coronary vasospastic disorders, cardiac arrhythmias, systemic hypertension, atherosclerosis, dilated and hypertrophic cardiomyopathies, abnormal cardiac diastolic function, migraine, subarachnoid hemorrhage, esophageal dysfunction and Raynaud's syndrome. In addition, the role of abnormal calcium fluxes in causing cellular damage during ischemia involving myocardium and neural tissues is considered, as is the potential use of calcium-channel blocking drugs in the treatment of myocardial infarction and stroke. Other articles explore the uses of these drugs in preserving myocardium during cardiopulmonary bypass, and in the treatment of pulmonary hypertension and asthma.

This symposium is the result of the thought, effort and studies of many persons. We hope that it will provide a stimulus for further studies that will permit a more fundamental understanding of the processes controlling both normal and abnormal cellular functions, and provide information leading to the more effective clinical use of calcium-channel blocking drugs.

Basic Cellular Mechanisms of Action of the Calcium-Channel Blockers

ARNOLD M. KATZ, MD

Calcium-channel blockers inhibit the entry of calcium ion (Ca^{++}) into excitable cells, including those of coronary and peripheral arterial smooth muscle and the heart. The ability of these drugs to block Ca^{++} entry into cells inhibits the essential role of this cation as an intracellular messenger. The effects of calcium-channel blockers on the heart include a negative inotropic effect on the working myocardial cells of the atria and ventricles. Because the upstroke of the action potential in these regions of the heart, and in the rapidly conducting cells of the His-Purkinje system, is due to a fast, sodium-dependent ionic current, calcium-channel blockers do not inhibit conduction in these cells. In the sinoatrial and atrioventricular (AV) nodes, on the other hand, depolarization is due primarily to a Ca^{++}-dependent slow inward current; as a result, the calcium-channel blockers inhibit the sinus pacemaker and AV conduction. Because our knowledge of the molecular structure of the calcium channels in the heart and smooth muscle is rudimentary, little is known of the molecular mechanisms by which calcium-channel blockers inhibit Ca^{++} entry across the sarcolemmal membranes in these cells. It is apparent, however, that the actions of different members of this class of drugs on the sarcolemma are not the same. Indirect evidence indicates that some members of this class of drugs may interact with hydrophobic regions of the proteins that make up, or regulate, the calcium channels in the plasma membrane. Work now in progress to define the precise sites of action of these drugs holds promise for the future development of new blockers with enhanced selectivity for calcium channels in specific cell types, making it possible to inhibit excitation-contraction or stimulus-secretion coupling in a given organ.

(Am J Cardiol 1985;55:2B–9B)

Calcium-channel blockers represent a new class of drugs that have found wide acceptance in the treatment of cardiovascular diseases. Unlike other currently available drugs, the therapeutic actions of these agents arise from their ability to inhibit directly the influx of calcium ion (Ca^{++}) across the plasma membranes of excitable cells. In the cardiovascular system, inhibitory effects are found in arterial smooth muscle—both coronary and peripheral—as well as in the heart. Because they affect tissue other than the heart and vasculature, calcium-channel blockers have considerable potential for use in other diseases.

The basis for these effects lies in the ability of these drugs to block Ca^{++} entry into cells, and thus to prevent this critical messenger from reaching sites within the cell that initiate, or regulate, key cellular processes. Because Ca^{++} is prevented from serving its essential role as an intracellular messenger, the term "calcium antagonist" is often used to describe these drugs. However, the calcium-channel blockers do not themselves antagonize the effects of Ca^{++}; instead, they prevent this ion from gaining access to its intracellular sites of action.

From the Division of Cardiology, University of Connecticut Health Center, Farmington, Connecticut. This study was supported in part by research Grants HL-22135, HL-21812 and HL-26903 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Arnold M. Katz, MD, Division of Cardiology, University of Connecticut Health Center, Farmington, Connecticut 06032.

Role of Calcium in the Cardiovascular System

Ca^{++} plays a key role in regulating the mechanical and electrical properties of both cardiac and vascular smooth muscle. This is because Ca^{++} serves both as a *chemical* signal that binds to proteins within the cell, and as the carrier of an *electrical* charge across the sarcolemma.

Calcium as a chemical messenger: In cardiac muscle, the role of Ca^{++} as an activator of contraction arises from its ability to initiate and modulate the interactions of the contractile proteins. These important functions of Ca^{++} are made possible by the very low Ca^{++} concentrations found within the resting myocardial cell, coupled with the presence in the cytosol of a family of high-affinity Ca^{++}-binding proteins. These proteins recognize the arrival of Ca^{++} within the cell

interior as a signal that generally either initiates or amplifies a cellular process.[1]

Ca^{++} also plays a central role in the initiation of smooth muscle contraction. As in the heart, this effect arises from the binding of Ca^{++} to a Ca^{++}-receptor protein of the contractile machinery. Ca^{++}-activated processes are also found in nonvascular smooth muscle and in a variety of nonmotile cells. The ability of the calcium-channel blockers to inhibit many of these Ca^{++}-dependent activation processes has been the basis for a growing number of clinical studies in which these drugs have been tested for their potential use to prevent or treat disorders arising from these Ca^{++}-activated processes.

Calcium as the carrier of an electrical signal: In addition to serving as a chemical messenger, the positively charged Ca^{++} carries an inward (depolarizing) current across the cardiac cell membrane.[2] The onset and decay of this current are slow, relative to the inward current carried by sodium (Na^+); hence this Ca^{++} current is often called the "slow inward current." In the working cells of the atria and ventricles, and in the rapidly conducting cells of the His-Purkinje system, Ca^{++} entry across the sarcolemma generates an inward current that contributes to the plateau of the action potential, which follows the primary depolarizing event arising from Na^+ entry through the fast inward current. In the pacemaker cells of the sinoatrial (SA) node and in the slowly conducting cells of the atrioventricular (AV) node, both of which lack active Na^+ channels, the inward current carried by Ca^{++} represents the major depolarizing mechanism. For this reason, Ca^{++} is responsible for normal pacemaker activity and AV conduction.

Provision of Activator Calcium in the Heart

During the process of excitation-contraction coupling, in which depolarization of the sarcolemma initiates contraction through the provision of Ca^{++} for binding to the contractile proteins, at least 2 mechanisms contribute to the appearance of activator Ca^{++} within the myocardial cell. A small amount of this ion moves across the sarcolemma from the extracellular space. This important activation process does not require the direct expenditure of energy because the Ca^{++} concentration in the extracellular space is approximately 10^{-3} M; during diastole, Ca^{++} concentration in the cytosol is approximately 10^{-7} M. The adult mammalian heart also contains a store of Ca^{++} in an intracellular membrane system, the sarcoplasmic reticulum (Fig. 1). Although the Ca^{++} concentration in the sarcoplasmic reticulum is not known with certainty, it is probably between 10^{-4} and 10^{-3} M and therefore much higher than that in the cytosol of the heart during diastole. Thus, as is the case of the flux of activator Ca^{++} across the sarcolemma, the movement of activator Ca^{++} out of the sarcoplasmic reticulum is a passive process.

According to one theory of excitation-contraction coupling, the influx of a small amount of Ca^{++} across the sarcolemma triggers a much larger Ca^{++} release from the sarcoplasmic reticulum ("calcium-triggered calcium release") that provides the large amount of Ca^{++} needed for binding to the contractile proteins and thus for the initiation of cardiac systole.[3,4]

Because both of the Ca^{++} fluxes that initiate cardiac systole are from a region of high Ca^{++} concentration (either in the extracellular space or in the sarcoplasmic reticulum) to one of much lower Ca^{++} concentration, the delivery of Ca^{++} to the cardiac contractile proteins is due largely to an increase in the Ca^{++} permeability of the sarcolemmal and sarcoplasmic reticulum membranes. It is generally assumed that these movements of Ca^{++} take place through "channels" that open in these membranes, as both of these membranes are themselves poorly permeable to this ion.

The complex nature of the mechanisms that regulate

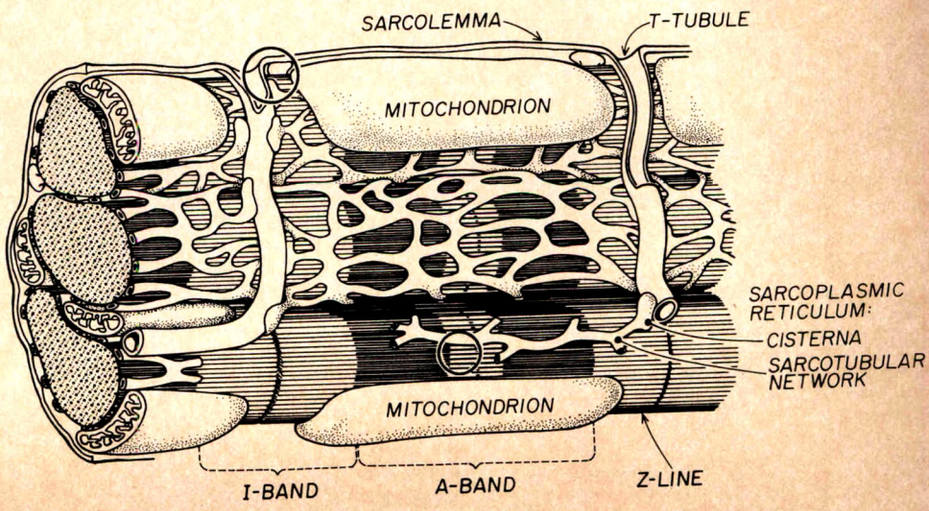

FIGURE 1. Ultrastructure of working myocardial cell. **Left,** contractile proteins are arranged in regular array of thick and thin filaments (cross-section). A-band represents region of sarcomere occupied by thick filaments into which thin filaments extend from either side. I-band is region of sarcomere occupied only by thin filaments; these extend toward center of sarcomere from Z lines, which bisect each I-band. Sarcomere, the functional unit of contractile apparatus, is region between each pair of Z-lines; it contains 2 half I-bands and 1 A-band. Sarcoplasmic reticulum, a membrane network that surrounds contractile proteins, consists of the sarcotubular network at center of sarcomere and cisternae, which abut on T-tubules and sarcolemma. Transverse tubular system (T-tubules) is lined by membrane that extends from sarcolemma and carries extracellular space into myocardial cell. Mitochondria are shown in central sarcomere and in cross-section at left. Reproduced with permission from *N Engl J Med* 1975;293:1184–1191.

the delivery of activator Ca^{++} to the cytosol is shown schematically in Figure 2, which contrasts the voltage-dependent calcium channels in striated muscle (Fig. 2A) with the more elaborate mechanism involving both voltage-dependent and receptor-operated calcium channels found in smooth muscle and nonmotile excitable cells (Fig. 2B). The top diagrams in both Figure 2A and 2B show the relatively simple mechanism by which activator Ca^{++} derived from the extracellular fluid reaches the cytosol by way of voltage-dependent calcium channels in the plasma membrane of striated muscle, or through either voltage-dependent or receptor-operated calcium channels in smooth muscle and nonmotile tissues.

More complex mechanisms involving activator Ca^{++} derived from intracellular stores are depicted schematically in the bottom part of Figure 2. In striated muscle (Fig. 2A), the release of activator Ca^{++} stored in the sarcoplasmic reticulum can be initiated by a small Ca^{++} entry (calcium-triggered calcium release, described earlier), or by a change in membrane voltage (depicted as Na^{+} entry through a sodium channel in the plasma membrane). Similarly, calcium release from an intracellular store in smooth muscle and nonmotile tissues can be initiated by an electrical signal or by Ca^{++} entry through voltage-dependent calcium channels as shown in the bottom part of Figure 2B. The calcium that initiates a calcium-triggered calcium release can also enter the cytosol of these tissues by way of receptor-operated calcium channels, and other messengers have been proposed to signal the release of calcium from intracellular stores.

Properties of the Calcium Channels in the Sarcolemma and Sarcoplasmic Reticulum

The membranes of the sarcolemma and sarcoplasmic reticulum are instrumental in controlling the Ca^{++} fluxes that are responsible for excitation—contraction coupling in the adult mammalian heart.[5] Each represents a barrier that separates the cytosol, in which maintenance of a low Ca^{++} concentration is essential for cell viability, from the regions of high Ca^{++} concentration in the extracellular space and the sarcoplasmic reticulum. Ion channels in both membranes regulate the "downhill" flux of Ca^{++} into the cytosol, although the properties of these ion channels and their sensitivities to calcium-channel blockers differ markedly.[6] The sarcolemmal and sarcoplasmic reticulum membranes also contain mechanisms that allow Ca^{++} to be transported from the cytosol into the extracellular space and lumen of the sarcoplasmic reticulum, respectively. As Ca^{++} transport out of the cytosol is against a concentration gradient, the mechanisms responsible for these active fluxes differ fundamentally from those that control passive Ca^{++} movements through the ion channels described previously.

Ca^{++} fluxes across the sarcolemma: The entry of Ca^{++} from the extracellular fluid is mediated by voltage-dependent ion channels in the sarcolemma, and by a sodium/calcium exchange mechanism. The latter in-

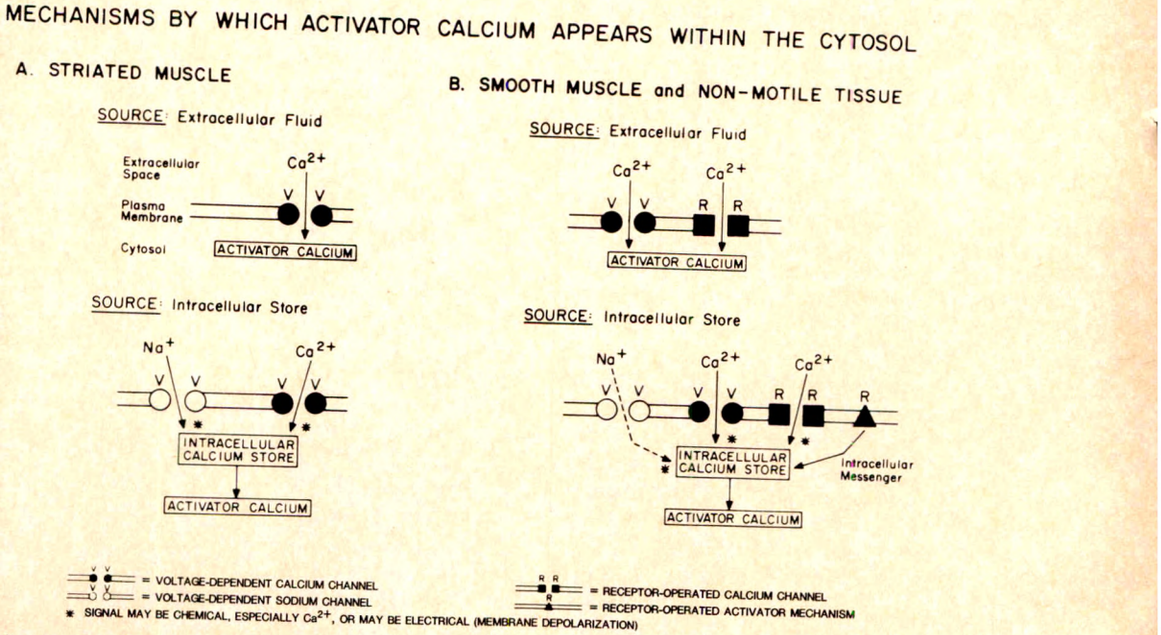

FIGURE 2. Schematic diagram showing mechanisms that can provide for delivery of activator Ca^{++} for excitation-contraction and stimulus-secretion coupling. (**A**) **Striated muscle:** in some amphibian and embryonic mammalian hearts, activator Ca^{++} is derived mainly from the extracellular fluid when this ion crosses the plasma membrane through voltage-sensitive calcium channels (**upper diagram**). In the adult mammalian heart (**lower diagram**), most of activator Ca^{++} is derived from intracellular stores in the sarcoplasmic reticulum from which Ca^{++}-release can be initiated when a small amount of this ion crosses the plasma membrane, or as a result of membrane depolarization. (**B**) **Smooth muscle and nonmotile tissue:** activator Ca^{++} derived from the extracellular fluid (**upper diagram**) can enter the cell through voltage-dependent calcium channels, one or more types of receptor-operated calcium channels or both. In many of these cell types, all or a portion of the activator Ca^{++} is derived from intracellular stores (**lower diagram**). Release of activator Ca^{++} from these stores can be induced by Ca^{++} entry through voltage-dependent or receptor-operated calcium channels, by membrane depolarization (which itself can be due to a calcium current), by other intracellular messengers released by plasma membrane or by any combination of these mechanisms.

volve a putative carrier that can bind either 1 Ca^{++} or 2 to 3 Na^{+} ions, and is able to move both cations in either direction across the sarcolemma. In addition to sodium/calcium exchange, which represents the most important mechanism that transports Ca^{++} out of the myocardial cell, the cardiac sarcolemma contains an adenosine triphosphate (ATP)-dependent Ca^{++} pump that directly links the liberation of chemical energy of ATP to the active transport of Ca^{++}.

As has already been discussed, Ca^{++} influx through the sarcolemmal-calcium channels represents a passive ion flux in which the cation moves down an electrochemical gradient from a region of high activity outside the cell to a region of low Ca^{++} activity within the cell. Sodium/calcium exchange, on the other hand, represents a countertransport mechanism in which the movement of 1 calcium ion in either direction is coupled to the movement of 2 or, more likely, 3 sodium ions in the opposite direction across the sarcolemma.[7] In this way, active Ca^{++} efflux from the cytosol is made possible by the energy derived from the downhill Na^{+} entry into the cytosol. This Na^{+} is pumped out of the cytosol by the sodium pump (Na-K ATPase).

Neither the calcium channel, the sarcolemmal Ca^{++} pump nor the putative sodium/calcium exchange carrier has been purified from cardiac muscle, so the biochemical properties of these transport mechanisms can only be deduced from the physiologic and pharmacologic properties of the transport processes themselves.

Ca^{++} fluxes across the sarcoplasmic reticulum: The mechanisms responsible for Ca^{++} fluxes across the intracellular membranes of the sarcoplasmic reticulum differ from those found in the sarcolemma. As is the case for the active transport of Ca^{++} across the sarcolemma, the sarcoplasmic reticulum contains an ATP-dependent Ca^{++} pump.[8] It appears, however, that these 2 Ca^{++} pumps are not the same. Much less is known of the mechanism by which this ion moves passively out of the sarcoplasmic reticulum.[9]

Structural Features of the Voltage-Sensitive Calcium Channel in the Sarcolemma

The membranes that control the movements of Ca^{++} from one region of the heart to another must possess 2 functional properties: they must provide a barrier that impedes the free movement of the ion between aqueous compartments, and they must contain structures that permit Ca^{++} movements from one side of the membrane to the other. As we shall see, much more is known of the structure of the barrier than of the mechanisms that control the movements of this ion across the barrier.

The membrane bilayer: The Ca^{++} impermeable barriers that separate the aqueous compartment of the cardiac cell interior (the cytosol) from those of the extracellular space and interior of the sarcoplasmic reticulum are lipid bilayers composed of phospholipid molecules. These bilayers can be viewed as ion-impermeable lipid sheets that are lined on either side by charged groups that interact readily with the aqueous compartments on either side of the membrane. Within the bilayer is a highly hydrophobic region, made up of hydrocarbon chains of the fatty acid moieties of membrane phospholipids, that serves very effectively to restrain the movements of ions such as Ca^{++}.

At the present time, most important biologic properties of a membrane, including the ability to transport ions, can be attributed to the proteins that lie within the bilayer. These intrinsic membrane proteins, which are firmly attached to the membrane bilayer, contain both hydrophylic regions that interact with the aqueous environments on either side of the membrane, and hydrophobic regions that are bound firmly within the hydrophobic fatty acyl chain region of the bilayer. These proteins can be imbedded in either half of the bilayer or, as is probably the case for ion pumps and channels, can span the bilayer so as to contact the aqueous compartments on both sides of the membrane.

Functional States of the Sarcolemmal Calcium Channels

The most important pathway for Ca^{++} entry across the sarcolemma is through calcium channels whose opening, closing and reactivation are under the control of the electrical potential across the membrane. Because the transitions between the open, closed and inactive states of these calcium channels are determined by membrane voltage, they are referred to as "voltage-dependent" channels. In addition to this voltage dependence, the transitions of the calcium channels in the cardiac sarcolemma at any membrane potential are governed by the intrinsic properties of the channel. Thus, the transitions of these channels are also "time dependent."

The time-dependent transitions in the cardiac sarcolemmal Ca^{++} channels are much slower than those of the fast sodium channels that are responsible for the initial depolarizing Na^{+} current in the working cells of the atria and ventricles, and in the rapidly conducting cells of the His-Purkinje system. For this reason, these calcium channels are often referred to as "slow channels."

The calcium channels of the cardiac sarcolemma differ from the sodium channels in another important respect—the voltage at which they begin to undergo their transition from the closed to the open state. Less depolarization is needed to initiate opening of the sodium channels than of the calcium channels. As a result, the calcium channels in the cells of the working myocardium and the His-Purkinje system begin to open only after the cell has already been partially depolarized by the rapid entry of Na^{+} through the sodium channels.

The working cells of the atria and ventricles and the fast conducting cells of the His-Purkinje system contain both sodium and calcium channels. In these cells, the delayed opening of the calcium channels, along with their relatively slow kinetics, cause the calcium channels to remain open after the initial, Na^{+}-dependent upstroke of the action potential has ended. In this way, the calcium channels generate an inward current that contributes to the plateau phase that is characteristic of the cardiac action potential in these regions of the heart. The fact that calcium channels are relatively insensitive to partial membrane depolarization, which can inactivate sodium channels, may permit the calcium

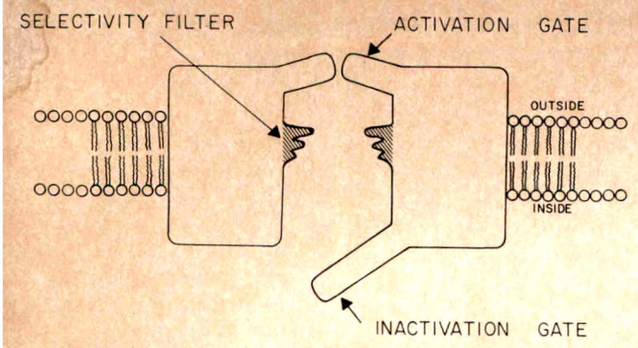

FIGURE 3. Schema of voltage-dependent ion channel in myocardial sarcolemma. The nature of the ion that can pass through open channel is determined by a "selectivity filter." Access of ions to channel is controlled by 2 different gating mechanisms. An "activation gate," which is closed in the resting state, opens in response to a change in transmembrane potential, thereby allowing ions to cross membrane. Closure of an "inactivation gate," which occurs at a slower rate in response to the same electrical signal that causes the activation gate to open, terminates the ion flux and inactivates the channel. The channel is reactivated when the activation gate has closed and the inactivation gate has reopened, both of which occur through voltage- and time-dependent processes. Reproduced with permission from *Am Heart J.*[12]

channels to initiate an action potential in partially depolarized cells, for example, in ischemic regions of the myocardium.

In the SA and AV nodes, where sodium channels are either absent or nonfunctional, the inward current carried by the calcium channels is entirely responsible for the action potential. This important feature, of course, determines the susceptibility of the sinus pacemaker and AV conduction to the effects of drugs that selectively block calcium channels.

Although some structural details are available regarding both the calcium pump of the sarcoplasmic reticulum,[10] which may also serve as a Ca^{++} channel,[9] and the rather nonselective channels connecting the interiors of adjacent cells across the nexus of the intercalated disk,[11] little is known of the structure of the voltage-sensitive ion channels of the cardiac sarcolemma. Several physiologic properties of these channels, however, allow certain key features to be schematized (Fig. 3).[12]

In view of evidence that these channels are highly specific for a given ion species, it can be assumed that the aqueous "pore" within the channel is provided with a selectivity filter that defines the type of ion that can pass through a given type of channel. Although the structure of the voltage-dependent calcium channels that generate the cardiac action potential is not known, their physiologic behavior gives some clues as to their molecular nature. In formulating a molecular model of an ion channel, the channel must be provided with a selectivity filter that determines its selectivity for the passage of a particular ion species (Fig. 3). In several cases, open ion channels appear able to contain more than one ion at any time. Thus, the passage of the ions through the channel can be viewed as the movement of a single file of ions, several of which are present at any time within the open channel.[13] Because the ions appear to move through the channel in their hydrated form, each open channel can contain several water-surrounded ions. One implication of this model is that the ion channel contains a series of barriers that interact with the hydrated ions as they pass from one side of the membrane to the other.

Because voltage-dependent ion channels can exist in different states, both open and closed, the model shown in Figure 3 is provided with "gates" that control the access of ions to the pore that crosses the membrane.

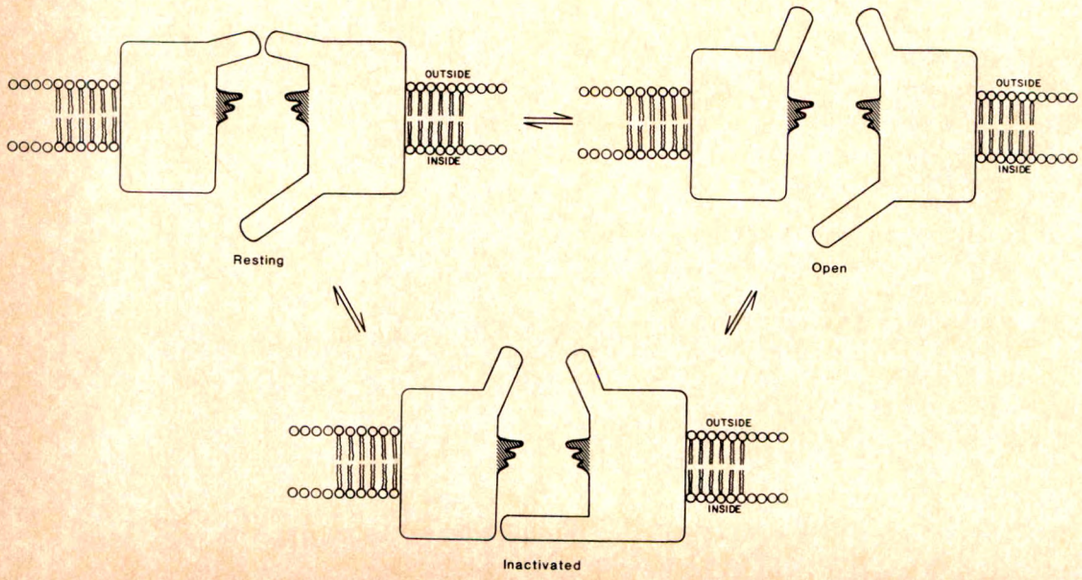

FIGURE 4. Three states of a voltage-sensitive ion channel are shown schematically using the diagram in Figure 3. In the resting channel, the activation gate is closed while the inactivation gate is open. A change in transmembrane potential initially opens the activation gate, thereby allowing ions to pass through the open channel. Subsequent closure of the inactivation gate causes the channel to become inactivated. Termination of the refractory state of the inactivated channel occurs when return to resting potential causes the inactivation gate to reopen and the activation gate to close. Reproduced with permission from *J Cardiovasc Med* 1983;8:435–452.

These gates appear to be charged regions of the channel proteins, because their ability to respond to changing transmembrane potential can be explained by the movement of charged structures in response to an alteration of the electrical field across the membrane. This hypothesis is supported by the ability of electrophysiologists to measure "gating currents." These currents, which are measured when membrane potential is abruptly changed under conditions in which transmembrane ion currents are eliminated, can be explained by the movement of charged structures within the membrane.[14] Thus, the opening and closing of the gates that control the access of ions to the interior of the transmembrane pore during the cardiac action potential can be explained by conformational changes of the channel proteins that result from the movements of charged regions of intrinsic membrane proteins comprising the ion channel.

To explain the physiologic properties of the voltage-dependent calcium channels of the cardiac sarcolemma, it is convenient to consider 3 states of the channel: resting, open and inactivated (Fig. 4). In the resting and inactivated states, Ca^{++} is unable to cross the membrane; in the open state, the gates are open and Ca^{++} can cross the membrane.

In the model shown in Figure 4, the movements of 2 types of gate are shown to control the transitions between these states of the channel. In the heart, calcium channels are closed when the cell is in its resting state and the interior of the cell is electronegative relative to the extracellular space. This resting state of the channel is shown with an *activation gate* closed and an *inactivation gate* open. Decrease of membrane potential, for example, when the approach of a propagated wave of depolarization or Na^+ entry through the fast inward current decreases electronegativity in the cell interior, causes the activation gate to open. This may be due to movement of a charged region of the channel, as has just been described. Once the channel is in its open or activated state, Ca^{++} ions can cross the membrane.

The open state of the calcium channel of the cardiac sarcolemma is quite brief and ends when, in response to sustained membrane depolarization, the inactivation gate closes the channel. However, the closed state of the calcium channel that terminates its open state differs from that of the resting channel. From a physiologic standpoint, the most important difference between these closed states is that in the resting cell membrane, the channel can open in response to membrane depolarization, whereas in the closed state that follows channel opening, the channel has become inactivated, or refractory, and can no longer open when the membrane is depolarized.

The inactivation gate is shown in the interior of the membrane in Figures 3 and 4, because it has been found in some cells that proteolytic enzymes added within, but not outside the cell can destroy the ability of the channel to become inactivated. According to this model, the transient opening of the calcium channel occurs during the brief interval between the rapid opening of the activation gate and the slower closing of the inactivation gate, both of which are initiated by membrane depolarization.

The return of the channel to its resting state does not occur until the resting membrane potential is restored and the interior of the cell is again electronegative. In the case of the calcium channels of the cardiac sarcolemma, this is brought about by the movement of potassium ions (K^+) out of the cell through its own K^+-selective channels. There is evidence that some of these repolarizing K^+ currents are initiated, or accelerated, by the appearance of Ca^{++} within the cell.[15] Once the cell interior again becomes electronegative, both the activation and inactivation gates return to their original resting states, thereby terminating the refractory state of the channel.

The voltage-dependent transitions of calcium channels in the cardiac sarcolemma are, in general terms, similar to those of the sodium channels that produce the initial rapid upstroke of the action potential in the cells of the His-Purkinje system and working atrial and ventricular myocardium. As has already been pointed out, however, the calcium and sodium channels differ in 2 important ways[16]: less depolarization is needed to activate and inactivate the sodium channels, and the rates of activation, inactivation and reactivation of the calcium channels are much slower than those of the sodium channels. Because conduction velocity is directly proportional to the rate of depolarization, propagation of Ca^{++}-dependent action potentials is slower than that of Na^+-dependent action potentials.

It must be emphasized that the model in Figures 3 and 4 is highly conjectural, and that other quite different models can also explain the physiologic properties of these channels.[17,18]

Actions of Drugs on the Calcium Channels in the Cardiac Sarcolemma

Several mechanisms have been proposed to explain the effects of drugs on calcium channels in the myocardium. From a molecular standpoint, perhaps the best understood are those caused by agents that increase cellular levels of adenosine 3′:5′-cyclic phosphate (cyclic AMP). These are probably mediated when the channel protein, or a protein that regulates its function, is phosphorylated by cyclic AMP-dependent protein kinases. In the case of the mechanism by which cyclic AMP regulates Ca^{++} transport across the membrane of the sarcoplasmic reticulum, phosphorylation of a 22,000 dalton protein called phospholamban leads to the acceleration of Ca^{++} fluxes carried out by the much larger, approximately 100,000 dalton, calcium pump ATPase protein.[19] There is also evidence that cyclic AMP-dependent phosphorylation increases the opening of calcium channels in the cardiac sarcolemma, although the molecular mechanism by which this occurs is poorly understood.[20]

In the case of calcium channels in smooth muscle and certain nonmotile excitable cells, the binding of neurotransmitters to their receptors can induce the opening of "receptor-operated channels." [21] Even less is known of the molecular basis for the operation of these channels than of the voltage-dependent channels described earlier. Clearly some sort of process is set into motion when an agonist binds to its receptor, but the nature of the molecular changes within the membrane that are

responsible for the eventual opening of a calcium channel is not known.

Another mechanism by which drugs are postulated to inhibit the flux of ions through a membrane channel is by insertion of the drug into the mouth of the channel. This mechanism has been proposed to explain the ability of membrane depolarization, which causes opening of the sodium channels, to enhance the potency of several antiarrhythmic drugs, including quinidine, that block these channels. A similar mechanism can explain the ability of verapamil and diltiazem to block calcium channels preferentially when the channels are in the open or inactivated state. This "use dependence" (that is, the potency of a drug to block the channels is enhanced when the channels have been "used") is most easily explained if the drugs enter the "mouth" of the channel preferentially during its open state. In the case of D600, an analogue of verapamil, evidence suggests that the drug binds preferentially at the inner, or cytosolic, opening of the calcium channel.[22]

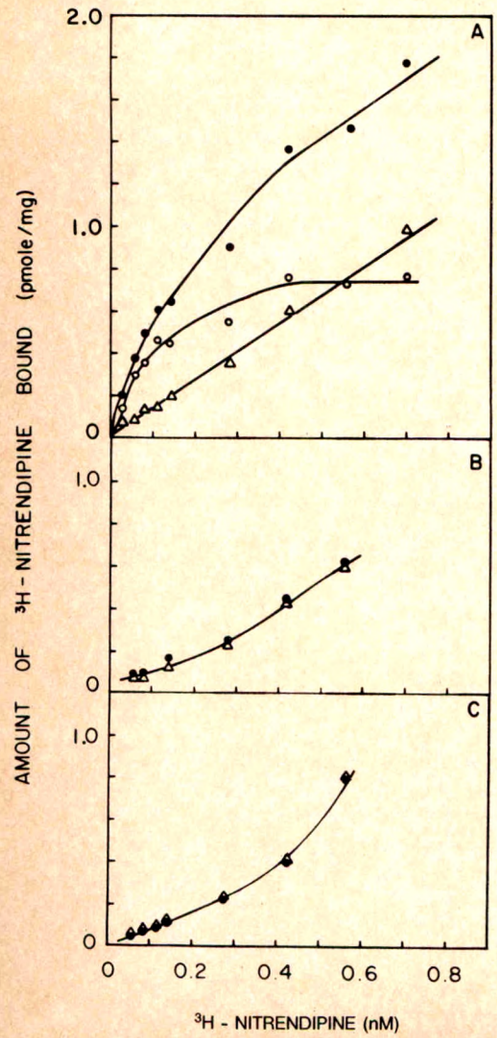

FIGURE 5. Total (**closed circles**), specific (**open circles**) and nonspecific (**open triangles**) binding of nitrendipine to (**A**) sarcolemmal, (**B**) sarcoplasmic reticulum and (**C**) mitochondrial membranes isolated from canine myocardium, as function of increasing concentrations of ^{3}H-nitrendipine. Reproduced with permission from *J Mol Cell Cardiol.*[25]

Yet another mechanism can explain some drug effects on the operation of sarcolemmal calcium channels. This is a nonspecific (local anaesthetic or "membrane stabilizing") action suggested by the hydrophobic nature of many membrane-active drugs, and involving interactions of the drug with hydrophobic regions of the membrane bilayer. These nonspecific interactions of a hydrophobic drug with the bulk membrane phospholipids can be mediated by incorporation of amphiphilic molecules into the membrane bilayer at regions remote from the intrinsic membrane proteins, where they may modify channel function through membrane expansion or other physical changes in membrane structure.[23] The resulting inhibition of channel function can thus be viewed as secondary to structural rearrangements within the membrane bilayer. Although hydrophobic interactions of drug molecules with the membrane bilayer can explain nonspecific effects of many drugs, they seem unlikely to explain *specific* actions of drugs on one or another class of membrane channels.

In contrast, the specific interaction of a drug with a given type of ion channel implies some recognition between the drug and the proteins that make up and regulate the channel. As has been indicated, these specific interactions could arise from a simple "plugging" of the channel mouth by the drug, or by a high-affinity interaction with a specific receptor site that is related to the channel. Because calcium-channel blockers often exert their actions at nanomolar concentrations, and stereospecificity has been observed,[24] it appears likely that they are recognized by specific structures of the calcium channel. The complexity of these interactions is highlighted by marked differences in the responses of Ca^{++} channels in different tissues, and even in the responses of different types of Ca^{++} channels in a given cell type, to a given calcium-channel blocking drug.[21] However, the wide variety of chemical structures that can block Ca^{++} channels more or less selectively argues against the tight binding of these drugs to a single class of "receptors" analogous to those that bind β-adrenergic agonists.

It is possible that the different chemical structures that share the ability to block calcium channels interact with hydrophobic regions of the channel proteins at sites in contact with the aqueous medium on the outside of the membrane. The large hydrophobic moieties of most of the calcium-channel blocking drugs, however, suggest that they may also interact with hydrophobic regions of the channel proteins, where they are imbedded in the fatty acyl chain region of the phospholipid bilayer. In either case, the changing sensitivity of the calcium channel to these drugs as the channel changes its state can be explained by a drug's preference for a given conformation of the channel. For example, verapamil's ability to block the channel is enhanced by prior depolarization of the membrane; this implies either that verapamil is bound within the open channel or that its strongest interaction with the channel proteins occurs when the channel is in its open state.

Differences in the susceptibility of various types of calcium channels to calcium-channel blocking drugs provides additional evidence for highly specific interactions between the calcium-channel blockers and the

structures whose function they inhibit. In general, receptor-operated calcium channels in smooth muscle, which open when a neurotransmitter or other agonist binds to its receptor on the sarcolemma, are less sensitive to these drugs than are voltage-dependent calcium channels that open in response to depolarization of the membrane.[21] As a result, excitation processes initiated by membrane depolarization are more likely to be inhibited by the calcium-channel blockers than would those excitation mechanisms that are mediated by neurotransmitters. As shown in Figure 2, however, the complexity and interplay of these mechanisms in smooth muscle make predictions based on this generalization rather risky.

Differences in sensitivity to the calcium-channel blockers are also found when similarly regulated calcium channels in different tissues are compared. For example, nifedipine is a much more potent blocker of voltage-dependent calcium channels in smooth muscle than in the heart; in contrast, the potency of verapamil in these 2 tissues is more similar.

The specific nature of the interaction between calcium-channel blocking drugs and cardiac membranes was demonstrated in a recent study from our laboratory that compared the ability of low concentrations of labeled nitrendipine, a calcium-channel blocker closely related to nifedipine, to bind to different membranes isolated from canine ventricles.[25] Nitrendipine bound specifically, and with high affinity, to sarcolemmal vesicles but not to membrane vesicles derived from the sarcoplasmic reticulum or to mitochondrial membranes (Fig. 5). This points to an interaction between nitrendipine and a structure present only in the sarcolemma, possibly the calcium channel itself or a protein involved in its physiologic regulation.

At present, few data allow the mechanism responsible for channel blockade to be defined in molecular terms. This question, however, is of considerable importance not only from its theoretical interest, but also from a practical standpoint. The practical implications of a clearer understanding of the molecular mechanism by which calcium-channel blockers exert their effects include the possibility that future research may allow calcium-channel blocking drug molecules to be "tailored" so as to block specific classes of calcium channel. This could lead to the development of drugs targeted to block calcium channels in one or another tissue. With such drugs, we would be able to inhibit specifically excitation-contraction or stimulus-secretion coupling in a given organ and so improve the specificity of treatment of diseases, like coronary vasospasm, that arise from abnormal calcium-channel function in one or another region of the body.

In conclusion, calcium-channel blockers inhibit Ca^{++} entry into excitable cells, including those of the coronary and peripheral arterial smooth muscle and heart. The ability of these drugs to block Ca^{++} entry into cells inhibits the essential role of Ca^{++} as an intracellular messenger.

The effects of the calcium-channel blockers on the heart include a negative inotropic effect on the working myocardial cells of the atria and ventricles. Because the upstroke of the action potential in these regions of the heart and in the rapidly conducting cells of the His-Purkinje system is due to a fast, sodium-dependent ionic current, the calcium-channel blockers do not inhibit conduction in these cells. In the SA and AV nodes, on the other hand, depolarization is due primarily to a calcium-dependent, slow inward current; as a result, the calcium-channel blockers inhibit the sinus pacemaker and AV conduction.

Our knowledge of the molecular structure of the calcium channels in the heart and smooth muscle is rudimentary, and little is known of the molecular mechanisms by which calcium-channel blockers inhibit the passage of Ca^{++} across the sarcolemmal membranes in these cells. It is apparent, however, that the actions of different members of this class of drugs on the sarcolemma are not the same. For example, nifedipine is much more potent as an inhibitor of calcium channels in smooth muscle than in the heart, whereas verapamil and diltiazem are approximately equipotent in the heart and vascular smooth muscle.

Although the precise molecular site of action of the calcium-channel blockers on the sarcolemma is not known, indirect evidence indicates that different members of this class of drugs act at different sites in these membranes, possibly with hydrophobic regions of the proteins that make up or regulate these channels.

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Comparative Effects of Calcium-Channel Blocking Agents on Left Ventricular Function During Acute Ischemia in Dogs With and Without Congestive Heart Failure

JOANN URQUHART, MD, STEPHEN E. EPSTEIN, MD, and
RANDOLPH E. PATTERSON, MD

To examine the relative potencies of verapamil, nifedipine and diltiazem on left ventricular (LV) function under ischemic conditions, 20 conscious closed-chest dogs that had partial occlusion of their circumflex coronary arteries were studied. Myocardial blood flow was measured by microspheres, LV function by radionuclide angiography. Drug effects were compared at doses causing equal decreases in mean arterial pressure (MAP) and in coronary vascular resistance of the nonischemic zone. Global ejection fraction (EF) and EF of the ischemic region were significantly decreased by verapamil ($p < 0.002$) and increased by nifedipine ($p < 0.001$); diltiazem caused no significant changes. Verapamil significantly increased peak diastolic filling rate ($p < 0.001$); nifedipine also increased diastolic filling rate but only at doses that markedly decreased MAP and coronary vascular resistance. Diltiazem was not significantly different from placebo. For doses causing an equal decrease in MAP, verapamil decreased heart rate ($p < 0.001$), and diltiazem and nifedipine increased heart rate ($p < 0.05$). Myocardial ischemic zone flow remained unchanged during placebo, verapamil, diltiazem or nifedipine infusion. To study the influence of heart failure on the hemodynamic effects of the calcium-channel blocking agents, 6 foxhounds underwent total occlusions of the left anterior descending coronary artery, resulting in myocardial infarction, volume loading to increase left atrial pressure and partial occlusion of the circumflex coronary artery. Verapamil depressed global left ventricular ejection fraction and increased left atrial pressure to as high as 40 to 45 mm Hg. In contrast, nifedipine decreased left atrial pressure and increased global EF. To evaluate whether the negative inotropic effect of verapamil or the positive inotropic effect of nifedipine was beneficial or detrimental to ischemic tissue, intramyocardial pH in dogs that had regional myocardial acidosis after acute coronary occlusion was studied. Pretreatment with verapamil decreased the degree of acidosis of ischemic myocardium as it depressed LV function, whereas nifedipine caused no change in the degree of acidosis as it increased LV function. These findings suggest that the negative inotropic effects of verapamil can protect ischemic myocardium.

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Verapamil, diltiazem and nifedipine are being used with increasing frequency in patients with angina pectoris caused by coronary artery disease. The antianginal mechanisms of these drugs remain uncertain, although they are known to have several hemodynamic and electrophysiologic effects that may contribute to their salutary actions. They are potent systemic vasodilators,[1] they possess negative inotropic potential[2] and verapamil and diltiazem can decrease sinus nodal automaticity and thereby decrease heart rate.[3–5] In addition, it is likely that varying degrees of coronary vasoconstriction may play a role in exacerbating coronary obstruction and thereby predispose the precipitation of angina pectoris in some patients with coronary atherosclerotic heart disease, even though they do not have severe coronary artery spasm.[6,7] Thus, the coronary vasodilator effects of calcium antagonists may also contribute to their antianginal effects.

Although each of the 3 calcium-channel blocking drugs approved for use in the United States exerts beneficial effects in patients with angina pectoris caused by coronary artery disease,[8–12] data have emerged suggesting that the relative potencies of these drugs

From the Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Joann Urquhart, MD, Cardiology Branch, National Heart, Lung, and Blood Institute, Building 10, Room 7B-15, National Institutes of Health, Bethesda, Maryland 20205.

differ in terms of their physiologic actions, that is, their electrophysiologic, vasodilator and negative inotropic effects. For example, several investigators[5,13,14] have shown that verapamil and diltiazem decrease sinus nodal automaticity and prolong atrioventricular conduction, thereby causing bradycardia. Mitchell et al[15] showed that although verapamil and diltiazem produce equivalent slowing of atrioventricular conduction, verapamil prolongs atrioventricular nodal refractoriness to a greater degree. Nifedipine, in contrast, has no direct electrophysiologic effect; it usually reflexly increases heart rate secondary to its hypotensive actions. In addition, although all 3 calcium-channel blocking agents are systemic vasodilators,[1] nifedipine is more potent by at least 1 order of magnitude. This has been shown by both in vitro and in vivo studies.[16–19]

Nifedipine, verapamil and diltiazem all have intrinsic negative inotropic properties that are most clearly demonstrated in studies using isolated muscle preparations.[2,20] Data show that the intracoronary injection of calcium-channel blockers at doses causing no systemic vasodilatation also causes negative inotropic effects.[21] However, as is the case with their electrophysiologic and vasodilator actions, the relative negative inotropic potencies of these 3 drugs differ considerably. A summary of these differences follows.

In isolated muscle preparations, nifedipine has the strongest depressant effect per molar concentration.[2,20] These results do not agree with those of most clinical studies, which demonstrate that nifedipine has minimal, if any, negative inotropic action.[22–26] In the experimental animal, Henry,[21] Weintraub[27] and their coworkers even reported improved shortening of ischemic myocardial segments with nifedipine. On the other hand, Walsh et al[28] found that in conscious dogs nifedipine had the strongest negative inotropic effect, when compared with verapamil and diltiazem.

Such disparities illustrate some of the difficulties in assessing the inotropic potential of a given drug and the relative potencies of different drugs. For example, when calcium-channel blockers are administered to animals in which reflexes remain intact, the emergence of their negative inotropic potential may become masked because of the confounding effects produced by alterations in afterload and changes in reflex stimulation to the heart. In addition to the effects exerted by differences in loading conditions and the degree of reflex stimulation to the heart, the disparities observed among the aforementioned studies may also relate to differences in methods used in assessing inotropic state, preparing the agents and dose of agent used. For example, Walsh et al[28] used equimolar doses of nifedipine, verapamil and diltiazem to compare effects. This approach ignores the fact that nifedipine is a much more potent vasodilator than either verapamil or diltiazem; hence, the clinically relevant dose of nifedipine that should be used in comparative studies would be much lower, on a milligram per kilogram basis, then the doses of verapamil or diltiazem. In this regard, no clinical studies and few experimental ones have used a wide range of doses of each agent. This would have permitted a comparison of the effects of these agents on left ventricular (LV) contractile function using dose-response curves, or at least doses that produce equivalent decreases in arterial resistance or pressure.

Millard et al[29] did use equi-effective vasodilator doses of verapamil, nifedipine and diltiazem, and found in conscious dogs that nifedipine exerted a positive inotropic effect and verapamil a negative one; diltiazem exerted little effect on contractile function. These results are important, but the observations were limited to animals not having myocardial ischemia. Assessing the relative effects of these drugs during ischemia is critical, because they are frequently used in such situations, and because it has been shown that, whereas verapamil may cause selective depression of ischemic myocardium,[30] no such effects have been associated with administration of nifedipine.

To examine the relative potencies of verapamil, nifedipine and diltiazem on LV function under ischemic conditions, we studied 20 conscious, closed-chest dogs.[31] We used such a model to avoid the effects of anesthesia or acute surgical trauma and to maintain reflex responses intact. The circumflex coronary artery was partially occluded in each dog before therapy with either placebo, verapamil, nifedipine or diltiazem, and the partial occlusion was maintained throughout the study. The dogs were studied in the conscious state during control conditions in the absence of myocardial ischemia, and then during partial occlusion before and during 4 doses of either saline solution placebo or 1 of the 3 calcium-entry blockers infused intravenously. After a 2-minute duration of a loading dose, each of 4 doses was administered intravenously for about 15 minutes. Loading doses were 30 μg/kg/min for verapamil and diltiazem, followed by infusions of 5, 10, 20 and 40 μg/kg/min respectively, for doses 1 to 4. The loading dose for nifedipine was 5 μg/kg/min, followed by infusions of 1, 2, 4 and 6 μg/kg/min, respectively, for doses 1 to 4.

Five dogs were studied in the placebo group, and 5 in each of 3 drug treatment groups. Myocardial blood flow was measured by radioactive microspheres, and LV function was measured by electrocardiogram-gated radionuclide angiography. The consequences of ischemia due to partial coronary occlusion were similar in all 4 groups. This similarity was assessed by comparing the absolute and relative changes between control and partial occlusion states before drug administration for myocardial blood flow, ejection fractions (EFs) and hemodynamic features.[31] When each of the 7 measured variables was ranked from least (1.0) to greatest (4.0) effect of partial occlusion, the mean rankings were not different: placebo (2.6), verapamil (2.6), diltiazem (2.4) and nifedipine (2.4 rank order units). Drug effects were compared at doses causing equal decreases in mean arterial pressure, and at doses causing equal decreases in coronary vascular resistance of the nonischemic myocardium.

We found that the 3 drugs differed markedly in their effects on LV function, during both systole and diastole. Most important, these different effects were evident at doses of each drug that exerted identical effects on mean arterial pressure or on coronary vascular resistance.

Nifedipine increased global EF and EF of the ischemic zone in parallel with its vasodilator actions (Fig. 1 and 2). Verapamil, in contrast, decreased both global and ischemic zone EF (Fig. 1 and 2) at doses that produced a vasodilator effect identical to that of nifedipine. Furthermore, the drugs exhibited different relative potencies when the minimal threshold dose required to cause vasodilation, as measured by a decrease in coronary vascular resistance, was compared with the threshold dose required to alter myocardial contractile function and LV diastolic filling.

Thus verapamil depressed myocardial contractile function, even at a dose that was not sufficient to alter aortic pressure or coronary vascular resistance (Fig. 2), a finding suggesting that the myocardium during ischemia may be more sensitive to the calcium-inhibiting actions of this drug than is vascular smooth muscle. It also suggests that a clinically safe dose of verapamil, in terms of its myocardial depressant effect, cannot be predicted on the basis of the drug's lack of effect on arterial pressure. The improvement in EF caused by nifedipine throughout its dose-response curve suggests that nifedipine, at least during mild ischemia, exerts no physiologically important myocardial depressant actions, and indicates that the direct myocardial depressant effects of nifedipine evident in vitro[2] may only occur at doses that result in more marked hypotension than achieved in our study. Moreover, the threshold dose at which EF increased was the same as that at which vascular resistance decreased (Fig. 2), a finding compatible with the concept that improved EF observed after nifedipine administration is caused by the afterload-reducing capacity of the drug and reflex sympathetic stimulation of the heart. Thus the direct myocardial depressant effects of nifedipine may be overshadowed in the intact animal by these indirect effects on cardiac function.

Although diltiazem decreases global EF at doses producing large decreases in coronary vascular resistance (Fig. 2), neither global nor ischemic zone EF was altered at doses producing no more than a 10- to 15-mm Hg decrease in arterial pressure (Fig. 1 and 2). This suggests that diltiazem, when administered in doses producing physiologic changes in arterial pressure and coronary vascular resistance, does not exert any net depressant effect on normal or mildly ischemic myocardium. However, if diltiazem were devoid of myocardial depressant activity, EF would be expected to increase because of the concomitant decrease in afterload, as was found with nifedipine. Hence our findings suggest that diltiazem does have negative inotropic effects during myocardial ischemia, a finding also suggested by the increase in left atrial pressure caused by the drug, from 8.8 ± 5.1 mm Hg after occlusion to 15.3 ± 5.1 mm Hg during dose 4 (Fig. 3). However, these negative inotropic effects, which are milder than those

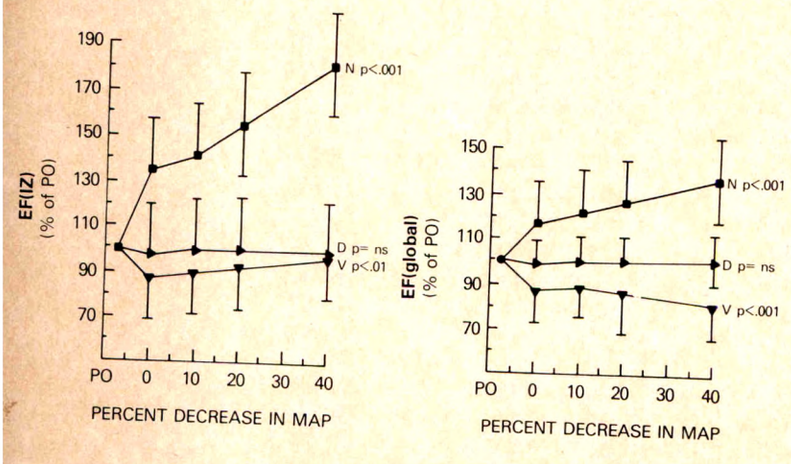

FIGURE 1. Comparison of drug effects at doses causing an equal decrease in mean arterial pressure (MAP). Ischemic zone (IZ) and global ejection fraction (EF) were increased by nifedipine (N), decreased by verapamil (V) and unchanged by diltiazem (D). **Bars** show 1 standard elevation. Change is presented as percentage of value during partial occlusion (PO) before drug administration. P values show results of analysis of variance in this and subsequent figures. Reprinted with permission from *Circulation.*[31]

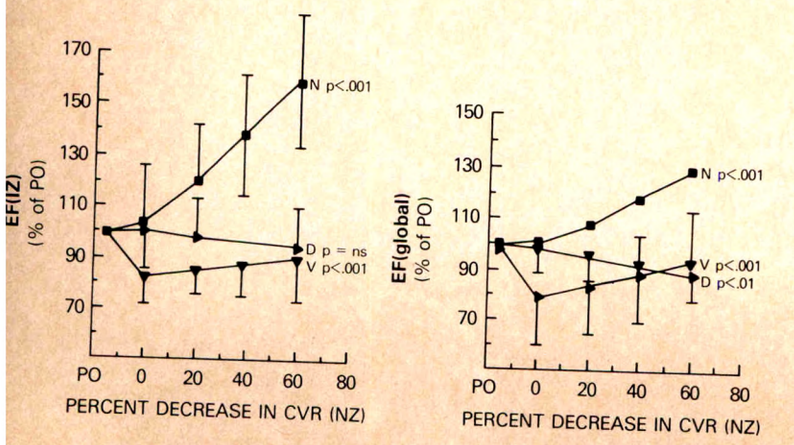

FIGURE 2. Comparison of drug effects at doses causing equal decrease in coronary vascular resistance (CVR). Ischemic zone (IZ) and global ejection fraction (EF) were increased by nifedipine, decreased by verapamil (V) and unchanged by diltiazem (D) except at very high doses, causing depression of EF. Change is presented as percentage of value during partial occlusion before drug administration. Reprinted with permission from *Circulation.*[31]

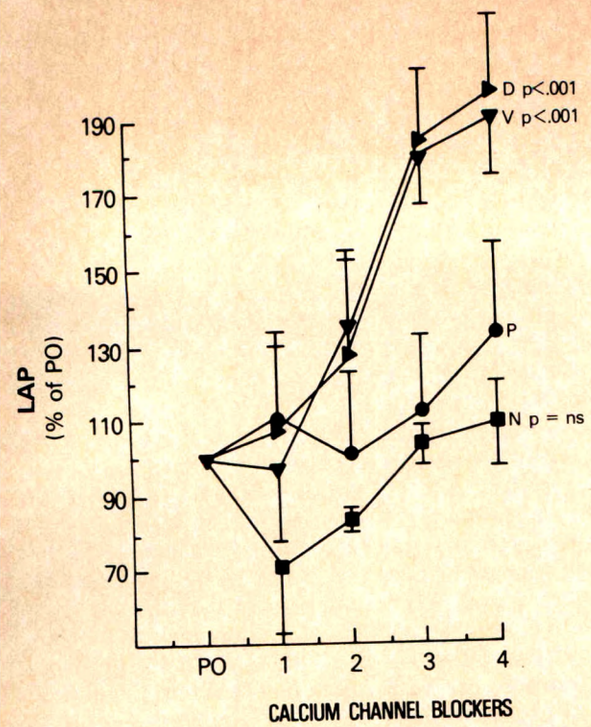

FIGURE 3. Comparison of dose response curves for left atrial pressure (LAP). Verapamil (V) and diltiazem (D) raised LAP compared with placebo (P). Nifedipine (N) was not different from placebo (P). Data are presented as percentage of value during partial occlusion before drug administration. Reprinted with permission from *Circulation.*[31]

of verapamil at doses causing comparable vasodilatation, are probably masked by the afterload-reducing actions of the drug and by the resulting sympathetic stimulation of the heart caused by baroreceptor reflexes.

In contrast to these results, Perez et al[32] found improved shortening of ischemic segments 20 and 80 minutes after total coronary occlusion in dogs treated with diltiazem to reduce aortic pressure by 5 mm Hg. Part of the difference between this study and ours may have been the use of open-chest versus awake closed-chested dogs. Further, Millard[33] noted improved shortening in the lateral border of normal tissue near an ischemic region (but not in the central ischemic region) with diltiazem in open-chest pigs; however, these borderline normal measurements are of uncertain significance.

It is also possible that our measurement of ischemic region EF by radionuclide angiography was less sensitive than the segment length measurements by ultrasound crystals used in those studies.[32,33] However, our measurements of ischemic regional function agreed with the ultrasound crystal method in studies of the effects of verapamil[30] and nifedipine.[21,27,32] Thus the different methods used to assess regional function may account for the difference between this and other studies[32,33] on the effects of diltiazem.

Differences in relative potencies of the 3 drugs on diastolic filling were also observed (Fig. 4). Partial coronary occlusion led to a marked impairment of peak diastolic filling rate, and verapamil administration led to large increases in the peak rate of diastolic filling. As with systolic cardiac function, verapamil improved diastolic filling at very low doses, that is, at doses that were insufficient to decrease mean arterial pressure or coronary vascular resistance. Although nifedipine also improved diastolic filling, it only did so at relatively higher doses, those that produced large decreases in mean arterial pressure and coronary vascular resistance. Further, the increases in diastolic filling rate produced by nifedipine was associated with a marked increase in heart rate, which by itself may increase diastolic filling rate. In contrast, the increase in diastolic filling rate produced by verapamil was associated with a decrease in heart rate. Diltiazem had no significant effect on diastolic function.

There is general agreement that verapamil, diltiazem and nifedipine increase coronary blood flow through normal coronary arteries as a result of vasodilation.[34–36] One of the most controversial areas, however, is the effect of calcium-channel blockers on coronary blood flow to ischemic myocardium. Henry et al[37] demonstrated an increase in myocardial blood flow to the lateral "border zone" with nifedipine, and interpreted this as representing an increase in collateral flow. This study did not consider the fact that the lateral border zone has been shown to be an admixture of normal and ischemic tissue, and therefore the increase in blood flow may in fact have represented an increase in flow to normal components of a sample composed of a mixture of nor-

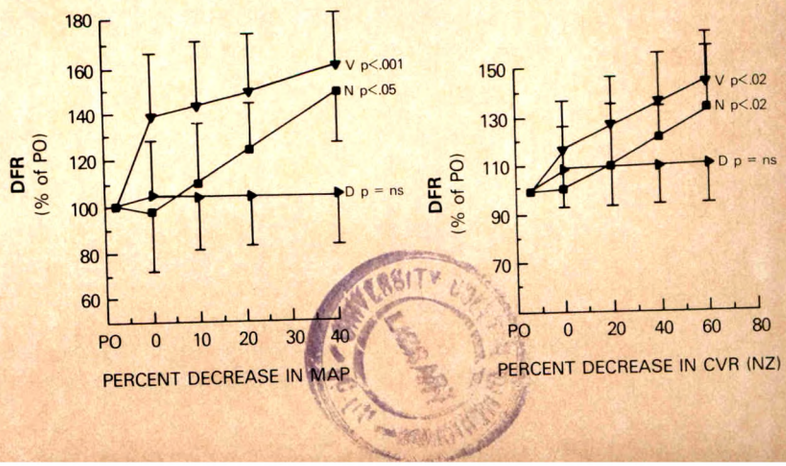

FIGURE 4. Comparison of drug effects at doses causing equal decrease in mean arterial pressure (MAP) and coronary vascular resistance (CVR). Verapamil (V) increased diastolic filling rate (DFR) at very low doses, whereas nifedipine (N) increased DFR only at high doses. Diltiazem (D) had no effect on DFR. Reprinted with permission from *Circulation.*[31]

mal and ischemic tissue.[38] Weintraub et al[39] took this admixture into account when analyzing their data from an open-chest model of partial occlusion, and showed that nifedipine increased subendocardial blood flow in the nonischemic zone, but decreased it in the ischemic zone. Bourassa et al[36] also used a model of partial occlusion and found that diltiazem increased coronary blood flow to the nonischemic area without changing flow to the ischemic tissue. These studies used models with total coronary occlusion, that is, regions of ischemia in which flow from collateral vessels may play an important role. Such results are probably not applicable to models of partial coronary occlusion, in which flow from collateral vessels probably plays a minor role.

We studied coronary blood flow in a model of partial occlusion in conscious dogs using a wide range of doses. Coronary vascular resistance in the normal zone did not change after partial coronary occlusion or during placebo infusion; however, it decreased significantly ($p < 0.001$) with nifedipine, verapamil and diltiazem (Fig. 5). Myocardial blood flow to the ischemic region measured by microspheres during partial coronary occlusion was 0.23 ± 0.03 ml/min/g, which was 18% of the blood flow to the normal zone. Ischemic zone flow remained unchanged during placebo, verapamil, diltiazem or nifedipine infusion (Fig. 5). Partial coronary occlusion decreased the ratio of subendocardial to subepicardial blood flow similarly in all groups, and no drug caused any significant changes in this ratio.

The lack of effect on flow to ischemic myocardium during partial coronary occlusion was most likely due to the fact that the arterioles of the ischemic zone were already maximally dilated and were therefore not susceptible to further dilatation. A second explanation may be that we studied the actions of these drugs under physiologic conditions, so that we made no attempt to control either arterial pressure (and thereby the distending pressure on the coronary artery) or heart rate. Decreases in the distending pressure of the coronary artery, particularly in partially occluded arteries, can cause passive increases in the resistance of the large epicardial artery.[40] Hence, it is possible that the coronary arterioles were dilated by the calcium-entry blocking agents, but that the resulting effect on total coronary vascular resistance was overridden by a concomitant passive increase in large vessel resistance caused by the decrease in coronary distending pressures.

Also, there usually is marked variability in myocardial blood flow when microsphere techniques are used.[41] This is particularly true when flow is measured in ischemic tissue.[42] This variability means that small changes in flow might be induced by these agents but they could not be detected by this technique. However, the direction of flow change after the administration of each drug was for blood flow to ischemic myocardium to decrease, although the changes were not significant. Thus in this model the calcium-entry blocker definitely did not improve blood flow to myocardium supplied by a fixed partial coronary occlusion.

We conclude that the relative potencies of the 3 calcium-channel blocking agents on LV systolic and diastolic function during myocardial ischemia are different when compared at the same level of vasodilator effect. Because verapamil and diltiazem depress myocardial contractility in the intact organism, even in the presence of only mild ischemia, their usefulness in the treatment of angina pectoris might sometimes be hazardous in

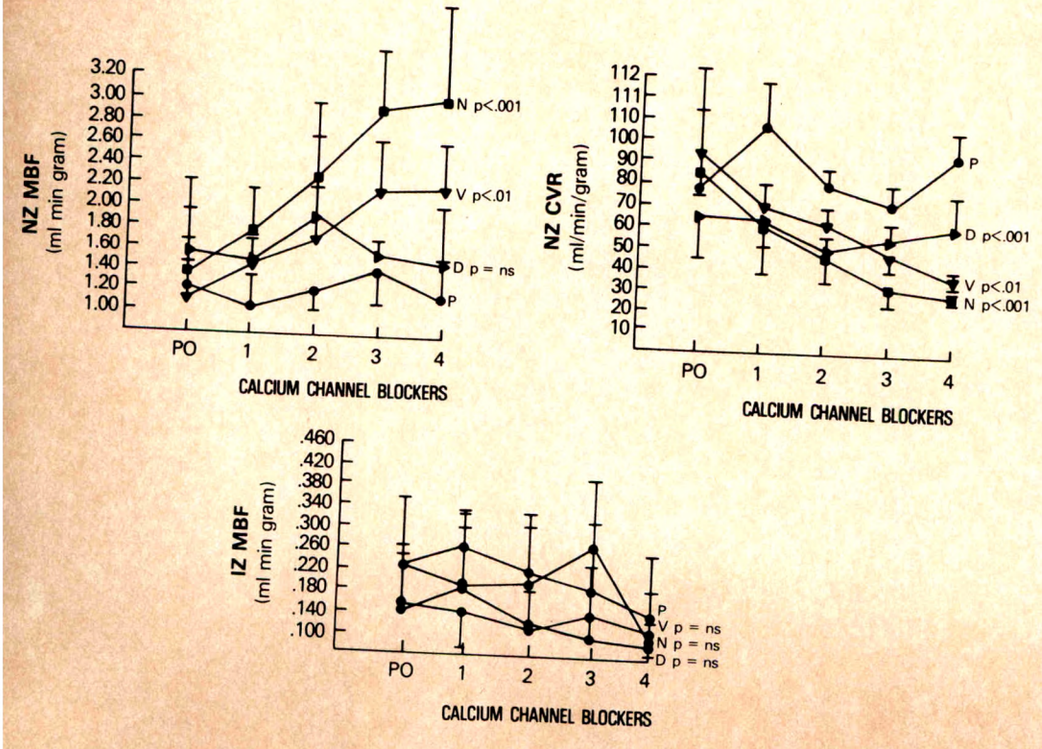

FIGURE 5. Comparison of dose-response curves for myocardial blood flow (MBF) to normal zone (NZ) myocardium and ischemic myocardium (IZ) and coronary vascular resistance (CVR) to NZ myocardium. Reprinted with permission from *Circulation*.[31]

patients with congestive heart failure. Thus Chew et al[43] demonstrated that in patients with severely decreased EF or increased pulmonary capillary wedge pressure, the short-term intravenous administration of verapamil caused further increases in the pulmonary capillary wedge pressure, and led to clinical deterioration.

On the other hand, Walsh et al[44] reported recently that large doses of diltiazem to decrease mean aortic pressure by 20 mm Hg improved LV function in 6 to 8 patients with severe congestive heart failure. It seems crucial, however, to reemphasize their conclusion: that this study of a small number of selected, carefully monitored patients does not establish the safety of calcium-entry blockers in the presence of LV dysfunction. For example, several of their patients had junctional rhythm during the study related to the dose of diltiazem.[44]

To study the influence of heart failure on the hemodynamic effects of the calcium-channel blocking agents, we performed studies in 6 foxhounds undergoing total occlusions of the left anterior descending coronary artery during anesthesia, resulting in myocardial infarction. Two weeks later, while awake, these dogs were volume-loaded to increase left atrial mean pressure to 12 to 15 mm Hg. The circumflex coronary artery was then partially occluded, and left atrial pressure increased to 25 to 30 mm Hg, while left ventricular ejection fraction (LV EF) decreased from 41 to 30%. Verapamil or nifedipine was then administered in graded intravenous doses and LV function was measured by radionuclide angiography. When matching decreases in mean arterial pressure were compared, verapamil depressed global LV EF and raised left atrial pressure to as high as 40 to 45 mm Hg. In contrast, nifedipine decreased left atrial pressure and increased global EF. Thus, verapamil has the potential to cause hemodynamically important deterioration in LV function, particularly in the presence of acute ischemia and LV failure.

While nifedipine has little or no negative inotropic effect when LV function and autonomic reflexes remain intact, hemodynamic compromise may be a problem in patients who are taking β-blocking agents, or who have chronic congestive heart failure; in both situations, cardiac function is compromised and autonomic nervous system adaptations are impaired. In this regard, failure occurring secondary to nifedipine administration has been reported when the drug is given with β-blocking agents,[45] and preliminary reports show that in patients with coexistent LV failure nifedipine has an important negative inotropic effect.[46]

Although the negative inotropic effects produced by verapamil on ischemic tissue can result in frank LV failure, particularly when the zone of ischemia is large, it is possible that the decrease in tension development of ischemic tissue produced by verapamil may actually decrease the degree of ischemia. To evaluate this question, we developed a fiber-optic probe to record intramyocardial pH in the beating heart of an anesthetized open-chest dog.[47] Our studies in dogs[48] that had regional myocardial acidosis after acute coronary occlusion indicate that pretreatment with verapamil reduces the degree of acidosis of ischemic myocardium as it depresses LV function. In contrast, pretreatment with nifedipine caused no change in the degree of acidosis of ischemic myocardium as it increased LV function. These preliminary findings suggest that the negative inotropic effects of verapamil can protect ischemic myocardium, presumably by decreasing its oxygen demand. On the other hand, although nifedipine improves LV function, it does not alter ischemic acidosis.

In conclusion, there are important differences in the hemodynamic effects of the different calcium-entry blocking drugs. First, verapamil appears to have the greatest potential for depressing LV function. Preliminary studies in an animal model of acute ischemia and heart failure show that verapamil may cause serious deterioration of LV function in the setting of congestive heart failure. On the other hand, decreasing contractile function of ischemic myocardium in the nonfailing heart may contribute to reducing ischemic injury by decreasing oxygen demand, and probably contributes importantly to the antianginal potency of verapamil. The negative inotropic effects of verapamil are also accompanied by an improvement in LV diastole function, which also probably contributes to the drug's salutary clinical effects. Diltiazem also depresses LV contractile function, although to a lesser extent than verapamil; thus, LV failure developing in an already decompensated heart after diltiazem administration is a distinct possibility. Nifedipine, on contrast, improves LV function in most patients, presumably by afterload reduction and baroreceptor-induced reflex mechanisms. However, recent reports have shown that nifedipine can cause LV dysfunction in patients with impaired sympathetic function caused by β-blocker therapy, and in patients with LV heart failure. Thus, each of the calcium-channel blockers has a different dose-response relation and different effects on LV systolic and diastolic function. As such, no drug is clearly "better" than any of the others. Rather, this diversity of action enables the physician to tailor therapy to the needs of the individual patient.

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Calcium-Entry Blockers, Vascular Smooth Muscle and Systemic Hypertension

PAUL M. VANHOUTTE, MD

Abnormal narrowing of the arterioles, caused by contraction of arteriolar smooth muscle, contributes to the genesis and the maintenance of the increased peripheral resistance observed in hypertension. Activation of the contractile process in vascular smooth muscle requires an increase in cytoplasmic calcium. In most blood vessels, the activator ion enters the cell through specific membrane channels, which can be inhibited by a chemically heterogeneous group of drugs, the calcium-entry blockers. The antihypertensive effect of these agents is probably explained by their inhibitory effect on (1) α-adrenergic activation (the pharmacologic subtype of postjunctional α-adrenoceptor does not necessarily determine the importance of calcium entry); (2) activation by nonadrenergic neurohumoral mediators (for example, serotonin); (3) acceleration of calcium entry by metabolites of arachidonic acid formed by lipoxygenase; and (4) inherent myogenic tone. **(Am J Cardiol 1985;55:17B–23B)**

In most patients with borderline or chronic hypertension, the cardiac output and the viscosity of blood are normal; the increase in arterial blood pressure is due to an augmented systemic vascular resistance. Thus, chronic arterial hypertension is now viewed as caused by the abnormal narrowing of the systemic resistance vessels.[1,2]

Vascular Responsiveness in Essential Hypertension

No single derangement is responsible for the increased systemic vascular resistance in essential hypertension (Fig. 1). Because the onset of hypertension is symptomless, the initiating factors may be obscured at the time it is detected by adaptations secondary to the long-term increase in arterial blood pressure.

In the early stages of hypertension, it seems likely that an exaggerated release of norepinephrine (NE) in the blood vessel wall contributes to increased arterial blood pressure. This conclusion is strengthened by the observations that removal of the sympathetic nervous system prevents the occurrence of hypertension in most animal models of the disease. Several factors may participate in the augmented sympathetic outflow to the vascular periphery, including abnormal activity of the higher nervous centers under the influence of stress or because of an augmented production of angiotensin II acting directly on the brain;[3] resetting of the mechanoreceptors governing the homeostatic control of blood pressure;[4] and greater than normal release of NE by the adrenergic nerve endings.[5,6] The latter can be due to inherent defects in the adrenergic neurons or to presence of neurohumoral mediators that facilitate the release or delay the disposition of the adrenergic transmitter, as could be the case for angiotensin II or circulating inhibitor(s) of Na^+, K^+ ATPase.[5–7]

The responsiveness of the vascular smooth muscle to the incoming sympathetic impulses can be modulated on both a short- and long-term basis. Among the circulating neurohumoral substances that can amplify vascular responsiveness to NE are angiotensin II and 5-hydroxytryptamine (serotonin).[8] To judge from experiments performed in animal blood vessels with cardiac glycosides, circulating inhibitor(s) of Na^+,K^+ ATPase would mainly prolong the effect of released NE and slow down the dilatation occurring upon cessation of sympathetic nerve activity.[7] Of the long-term important factors, structural adjustments of wall thickness, whether caused by water logging or proliferation of smooth muscle or both, probably play the major role. However, true hypersensitivity to vasoconstrictor agents, in particular NE, may also occur.[2,6] One of the consequences of long-term exposure of the blood vessel wall to increased pressure may be its premature aging, with a characteristic augmentation of the responsiveness to the contractile effect of serotonin.[9]

From the Department of Physiology and Biophysics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Address for reprints: Paul M. Vanhoutte, MD, Department of Physiology and Biophysics, Mayo Clinic and Foundation, Rochester, Minnesota 55905.

Calcium Entry and Vascular Smooth Muscle

Activation of the contractile process in vascular smooth muscle cells depends on the phosphorylation of myosin after activation of the myosin light chain kinase by the calmodulin-calcium complex. Thus, the cytoplasmic concentration of calcium is critical in determining the degree of interaction between actin and myosin, and hence the contractile state of the smooth muscle.[10–14] The cytoplasmic concentration of calcium is the result of a number of cellular processes with opposing effects (Fig. 2).

Increases in calcium concentrations can be brought about either by mobilization from cellular stores (for example, internal surface of the cell membrane, sarcoplasmic reticulum) or by increasing the permeability of the cell membrane. The latter is thought to be the consequence of the opening of specific channels (calcium channels) within the cell membrane. The opening of these channels can be induced either by changes in membrane potential (potential-operated channels), by binding of neurohumoral mediators to specific receptors of the cell membrane (receptor-operated channels) or by binding to a receptor followed by cell membrane depolarization. Cellular mobilization of calcium can be triggered by neurohumoral mediators in the absence of calcium entry.[15–21]

Decreases in cytoplasmic calcium concentrations follow the activation of active pumps such as Na^+,K^+ ATPase, Ca^{++} ATPase or Na^+,Ca^{++} exchange systems. These processes will relocate the ion into the cellular storage sites or move it to the extracellular space. The removal of calcium from the cytoplasm is accelerated by the production of cyclic nucleotides, in particular cyclic adenosine monophosphate, the hyperpolarization of the cell membrane or both.[1,10,12,22]

Calcium-Entry Blockers and Vascular Responsiveness: Vasoconstrictor Agents

Norepinephrine: The NE liberated by sympathetic nerve endings binds to postjunctional (postsynaptic) α-adrenoceptors, which in turn activate the contractile process. Depending on their affinity for a variety of agonists and antagonists, alpha-adrenoceptors can be subdivided into at least 2 subtypes (α_1- and α_2-adrenoceptors) (Fig. 3). The postjunctional α-adrenoceptors can belong to both subtypes.[23–25] This has been demonstrated in particular in intact animals and man, but can also be evidenced in isolated blood vessels.[26] The relative importance of the α_1- versus α_2-adrenergic component of the postjunctional action of catecholamines may vary, because it can be modulated by circulating substances or by local physical conditions. For example, angiotensin II[27] and inhibitors of Na^+ K^+ ATPase[7] may favor α_2-adrenergic activation. Local warming augments the responsiveness to α_1-adrenergic agonists but reduces α_2-adrenergically mediated responses.[28]

A remarkable feature of the response of vascular smooth muscle to NE is the heterogeneity among blood vessels from the same or different species concerning the dependence of α-adrenergic activation and the entry of extracellular calcium. As a consequence, the calcium-entry blockers can vary widely in their ability to inhibit NE-induced contractions in various blood vessels.[16,17,21,23,29–39] For example, in the canine saphenous vein, calcium-entry blockers only moderately depress the contractile response to exogenous norepinephrine (Fig. 4), phenylephrine or sympathetic nerve stimulation. The canine femoral and coronary arteries (Fig. 5) and the rabbit aorta are much more susceptible to inhibition of calcium-entry during α-adrenergic activa-

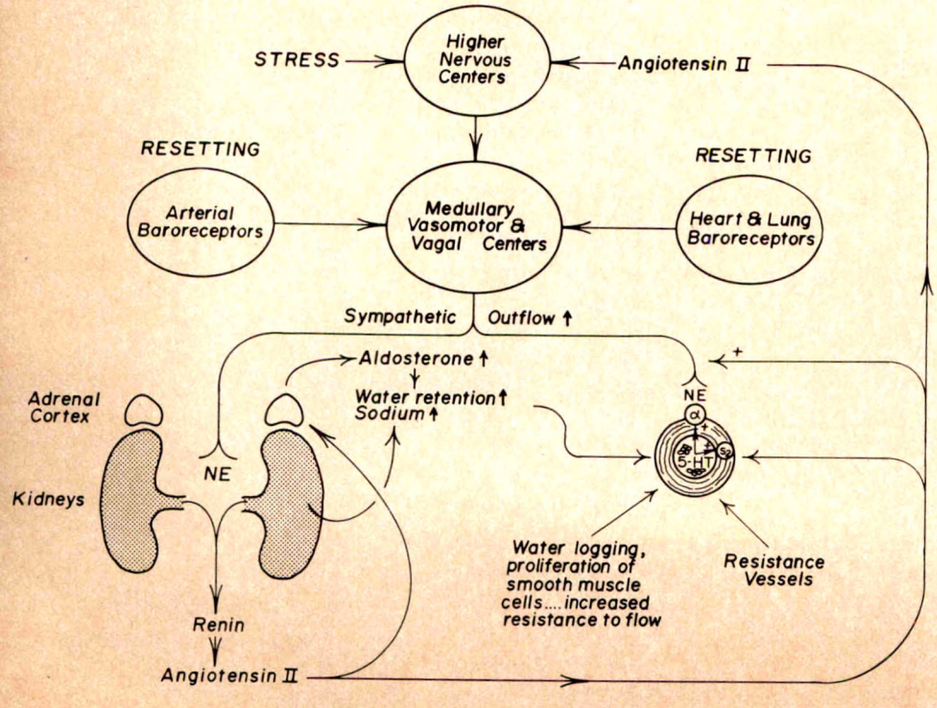


FIGURE 1. Factors that may be involved in genesis of increased peripheral resistance in essential hypertension. In many instances, sympathetic outflow is increased, particularly in early stages of the disease. In addition, for each level of sympathetic nerve activity, adrenergic nerve terminals may liberate more NE than normal and α-adrenoceptors of vascular smooth muscle cells may be more sensitive to transmitter. Possible interference of serotonin is shown either as direct effect on S_2-serotonergic receptors mediating contraction of vascular smooth muscle cells, or as amplifying effect (also mediated by S_2-serotonergic receptors) on response of vascular smooth muscle cells to other vasoconstrictor stimuli. For clarity, only α-adrenergic activation is mentioned. 5-HT = serotonin; NE = norepinephrine; ↑ = increase; and + = facilitation. Reprinted with permission from Butterworths.[2]

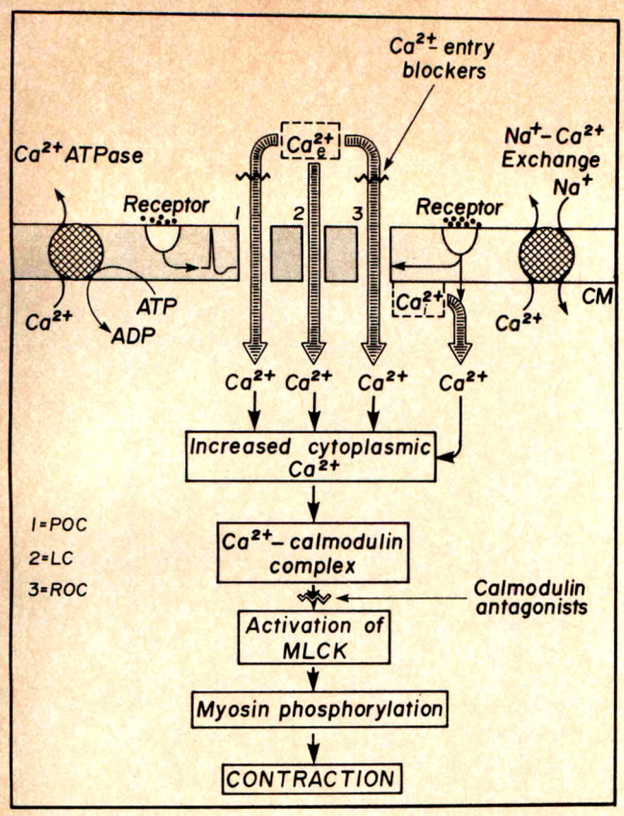


FIGURE 2. Calcium-dependent regulation of contractile activity in vascular smooth muscle. Cytoplasmic calcium (Ca^{++}) levels are increased by calcium influx through cell membrane (CM) potential-operated calcium channels (1 = POC), passive calcium "leak" pathway (2 = LC) (calcium entry that occurs under resting conditions) and receptor-operated calcium channels (3 = ROC). Receptor occupation by specific agonist (**closed circles**) may also induce release of calcium from intracellular storage sites or may depolarize cell membrane and activate potential operated channel. Calcium activates myosin light chain kinase (MLCK) by binding to calmodulin. Activated MLCK catalyzes phosphorylation of myosin, which increases actin-myosin interactions resulting in contraction. Cytoplasmic calcium levels are reduced through operation of cell membrane pumps, including Ca^{++}-ATPase (**far left**) and Na^{+}/Ca^{++} counter-transport (**far right**) that promote calcium efflux. **Closed wavy lines,** inhibited by calcium-entry blockers; **open wavy lines,** inhibited by hydrophobic compounds including pimozide and trifluoperazine. Reprinted with permission from *Int Angiol.*[14]

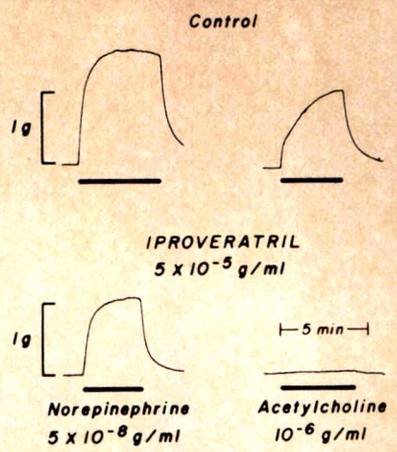


FIGURE 4. Response of same canine saphenous vein strip to norepinephrine (**left**) and acetylcholine (**right**) before (**top**) and after (**bottom**) inhibition of calcium entry with verapamil (iproveratril). Reprinted with permission from W. B. Saunders.[31]

tion. It is uncertain why calcium-entry blockers differentially affect the response of various blood vessels to alpha-adrenoceptor stimulation. One explanation is that the smooth muscle cells contain different proportions of postjunctional α_1- and α_2-adrenoceptors, which could be linked preferentially to either the entry of extracellular calcium or the mobilization of intracellular stores of the ion.[23,33] Thus, in canine arteries and in rabbit aorta, the postjunctional α-adrenoceptors are characterized as α_1 and appear to be linked preferentially to calcium entry (Fig. 5). However, in the isolated canine saphenous vein and in resistance vessels of pithed animals, certain postjunctional α-adrenoceptors possess characteristics of the α_2 subtype, and when activated also trigger the entry of extracellular calcium (Fig. 6). Thus, the varying degrees of the dependence of the response to NE upon calcium entry are not determined by the pharmacologic characteristics (α_1 or α_2) of the postjunctional adrenoceptors involved, but rather by the functional differentiation of the vascular smooth muscle.[23,32,34]

Nonadrenergic activation: Calcium-entry blockers inhibit constrictions of arteries, in particular cerebral

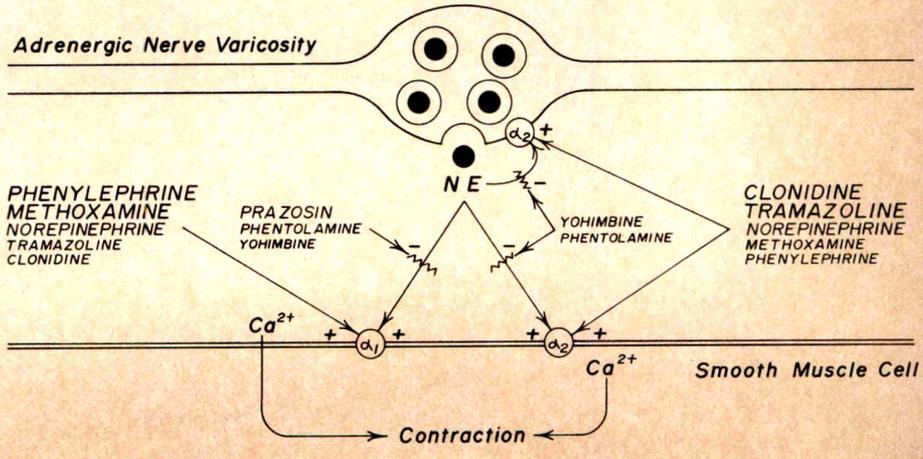


FIGURE 3. Interaction of released NE with pre- and postjunctional α-adrenergic receptors, and indication of affinity of these receptors for some agonists and antagonists. Size of letter types used for each substance indicates degree of affinity. NE = norepinephrine. Reprinted with permission from *J Cardiovasc Pharmacol.*[23]

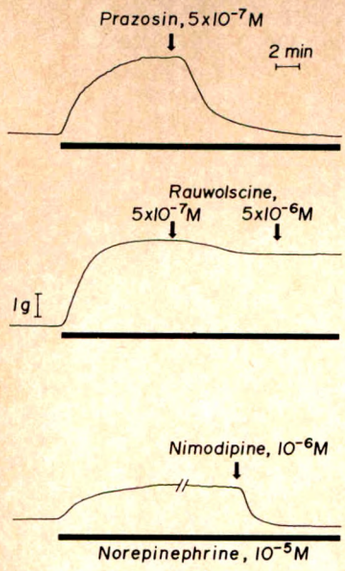


FIGURE 5. Effect of α_1-selective antagonist prazosin, α_2-selective antagonist rauwolscine and calcium-entry blocker nimodipine on contractions of canine coronary artery evoked by norepinephrine. Experiments were performed in presence of cocaine, hydrocortisone, propranolol and indomethacin to inhibit neuronal uptake, extraneuronal uptake, β-adrenoceptors and synthesis of vasodilating prostaglandins, respectively. Reprinted with permission from *J Pharmacol Exp Ther.*[32]

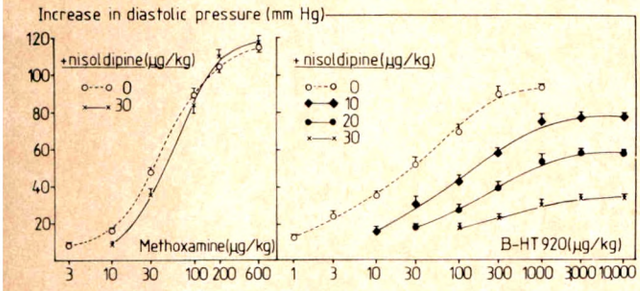


FIGURE 6. Log dose-pressor response curves to intravenous methoxamine (**left**) and B-HT 920 (**right**) in pithed normotensive rats after intraarterial pretreatment (15 minutes) with calcium-entry blocker nisoldipine. Note pronounced depression of slope and maximum of dose-response curve to B-HT 920 at very low doses of nisoldipine and negligible effect of this drug on hypertensive action of methoxamine. Reprinted with permission from *J Cardiovasc Pharmacol.*[33]

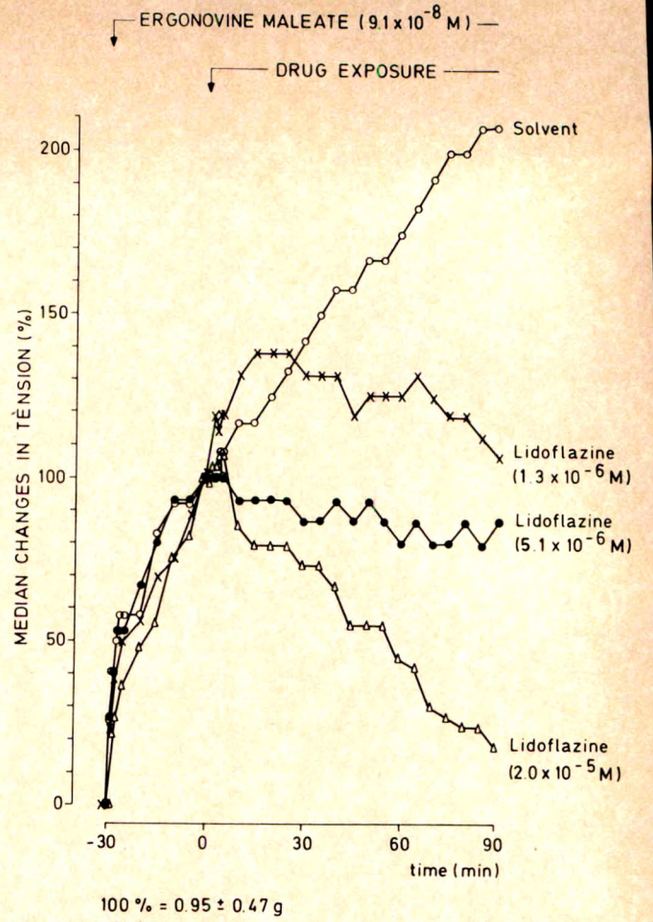
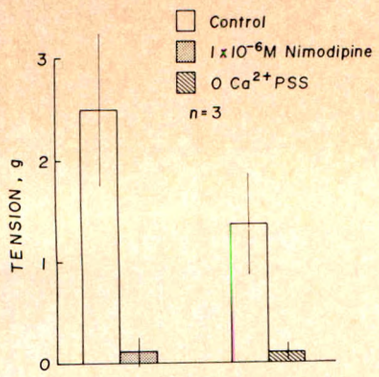


FIGURE 7. Effect of solvent and increasing concentration of calcium-entry blocker lidoflazine on contractile response of segments of coronary arteries to ergonovine maleate. Data are shown as median changes in tension and expressed as percent increase in tension above basal level upon treatment with solvent or lidoflazine. Reprinted with permission from *J Pharmacol Exp Ther.*[38]

and coronary arteries, caused by vasoconstrictor substances such as serotonin, ergonovine maleate (Fig. 7) and prostaglandin $F_{2\alpha}$.[16,17,21,23,29,30] In cutaneous veins, calcium-entry blockers that have little or no effect on the response to NE markedly inhibit the response to acetylcholine (Fig. 4). This demonstrates that in certain blood vessels, depending upon the cell membrane receptor involved, the activation of the contractile process relies to a varying degree upon the entry of extracellular Ca^{++}.

Ca^{++} Entry and Metabolism of Arachidonic Acid

Contractions of canine saphenous veins evoked by acetylcholine are augmented by inhibitors of cyclo-oxygenase; this augmentation is not observed in the presence of inhibitors of lipoxygenase and is inhibited by the calcium-entry blockers diltiazem and nimodipine.[40] Hypoxia augments the contractions of canine saphenous veins evoked by acetylcholine and this augmentation is blocked by calcium-entry blockers.[41] Contractions also occur in quiescent coronary arteries exposed to hypoxia,[42] in the same preparation, hypoxia greatly augments contractions evoked by NE and serotonin.[43] The hypoxic contractions of coronary smooth muscle are prevented by calcium-entry blockers (Fig. 8) and by inhibitors of lipoxygenase. These findings suggest that metabolites of arachidonic acid can modulate calcium entry.[40,42,44] Activation of cell membrane receptors or cell membrane depolarization accelerates the entry of calcium, which in turn triggers the contraction (Fig. 2). Calcium entry into the cell also activates phospholipase, and production of arachidonic acid results. Under normal conditions, arachidonic acid is metabolized through cyclo-oxygenase to prostanoids, which have varying effects on smooth muscle tone depending on the blood vessel considered. However, if cyclo-oxygenase is inhibited, either pharmacologically



IGURE 8. Effect of nimodipine (**left**) and calcium removal (**right,** 0 Ca^{++} SS) on hypoxia-induced contractions in canine coronary artery. Tenion was measured at peak of nitrogen-induced contraction. Nimodipine vas present for 40 minutes and calcium was removed from physiologic alt solution for 40 minutes. Reprinted with permission from Martnus-Nijhoff.[42]

or by tissue hypoxia, arachidonic acid is diverted through the lipoxygenase pathway. The end products of the action of this enzyme then in turn (and in an unknown way) greatly accelerate calcium entry, and thus favor contraction of the smooth muscle (Fig. 9).

Myogenic Tone

The arterioles are characterized by their propensity to develop myogenic tone; this phenomenon depends highly upon the influx of extracellular calcium. In certain isolated blood vessels, most notably portal-mesenteric veins of different species (Fig. 10 and 11), spontaneous rhythmic (myogenic) contractions that depend on availability of extracellular calcium can also be observed.[1,31] They presumably result from spontaneous depolarization of the cell membrane, which then opens calcium channels (Fig. 8). The degree of myogenic activity is dependent on the distension imposed upon the blood vessel wall (Fig. 10), in part because progressive distension causes depolarization of the cell membrane, bringing it closer to threshold for spontaneous action potentials. This relation helps to explain the maintenance of blood flow despite variations of arterial blood pressure (autoregulation).[1] This may be of particular importance in those cases of hypertension in which total body autoregulation contributes to the genesis of the disease.

Calcium-entry blockers inhibit the myogenic activity of portal-mesenteric veins with varying potencies, with the dihydropyridines (for example, nifedipine) being the most potent (Fig. 11).[16,17,29,44,45] Because the myogenic tone of the arterioles also depends upon the entry of extracellular calcium, it is not surprising that the calcium-entry blockers, which are the most potent inhibitors of spontaneous activity in portal-mesenteric veins, also cause the greatest decrease in peripheral vascular resistance in the intact organism, and hence are the most likely candidates as antihypertensive agents.

In summary, a number of chemically distinct pharmacologic agents, including cinnarizine, diltiazem, flunarizine, lidoflazine, methoxyverapamil, nifedipine and verapamil, can antagonize the entry of calcium during activation of vascular smooth muscle cells. However, because the source of calcium (entry or cellular mobilization) varies, depending on the anatomic origin of the vascular smooth muscle and the means by which it is activated, the effect of the calcium-entry blockers in antagonizing the contractile responses of isolated blood vessels may vary considerably. In large blood vessels, the main controller of vascular diameter is the sympathetic nervous system. The NE liberated by the adrenergic nerve endings binds to postjunctional alpha-adrenoceptors, which activate the contractile process. In certain arteries and veins, calcium-entry blockers only moderately depress the contractile response to exogenous NE or sympathetic nerve stimu-

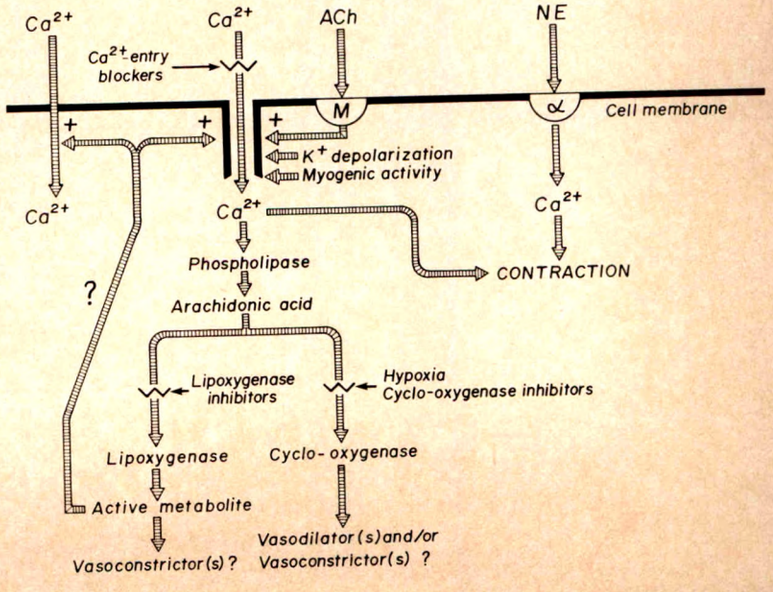


FIGURE 9. Proposed interaction between calcium entry and arachidonic acid metabolism in canine vascular smooth muscle. In saphenous vein, contractions induced by acetylcholine (ACh) and potassium (K^+) are inhibited by calcium-entry blockers, but potentiated by inhibitors of cyclo-oxygenase. Contractions induced by norepinephrine (NE) are only moderately reduced by calcium-entry blockers and are not augmented by inhibitors of cyclo-oxygenase. In coronary artery, hypoxia inhibits cyclo-oxygenase and induces a contraction that can be inhibited by calcium-entry blockers. Augmentation of entry of calcium by ACh, K^+ and hypoxia results in activation of phospholipase. Proposed arachidonic acid is diverted into lipoxygenase pathway (when cyclo-oxygenase is inhibited pharmacologically or by hypoxia), products of which in an unknown fashion enhance entry of calcium through calcium channel or possibly by acting as calcium ionophore. α = alpha-adrenoceptor; Ca^{++} = calcium; M = muscarinic receptor; + = augmentation; ? = unknown; wavy lines = inhibition. Reprinted with permission from Martinus-Nijhoff.[42]

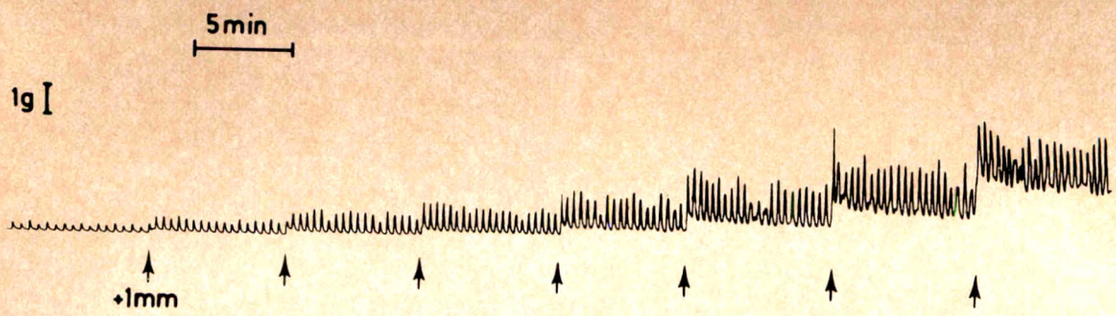


FIGURE 10. Progressive distension augments rate and amplitude of spontaneous contractions in canine portal-mesenteric vein. Reprinted with permission from W. B. Saunders.[31]

lation, indicating that in these smooth muscles catecholamines activate the contractile process mainly by enhanced cellular mobilization of calcium. However, most veins and arteries, including the coronaries, are very sensitive to inhibition of calcium entry during α-adrenergic activation. The reason for the differential effects of calcium-entry blockers on the response of various isolated blood vessels to α-adrenergic activation is still uncertain. Calcium-entry blockers inhibit contractions of most isolated arteries caused by nonadrenergic vasoconstrictor substances, such as serotonin, ergonovine maleate and prostaglandin $F_{2\alpha}$. In certain blood vessels, most notably the precapillary resistance vessels, the portal-mesenteric vein of different species and the human coronary artery, spontaneous activity is observed under control conditions. This myogenic activity depends on the availability of extracellular calcium and is presumably caused by spontaneous depolarization of the cell membrane, which then opens specific potential-operated calcium channels. Most calcium-entry blockers inhibit myogenic activity of vascular smooth muscle. However, the potency of the available compounds varies in this regard, with the dihydropyridines being the most potent. Because myogenic tone of the arterioles also depends upon the entry of extracellular calcium, it is not surprising that the calcium-entry blockers, which are most potent in inhibiting the spontaneous activity of portal-mesenteric veins, appear to cause the greatest decrease in peripheral vascular resistance in the intact organism, and hence are the most likely candidates for antihypertensive agents.

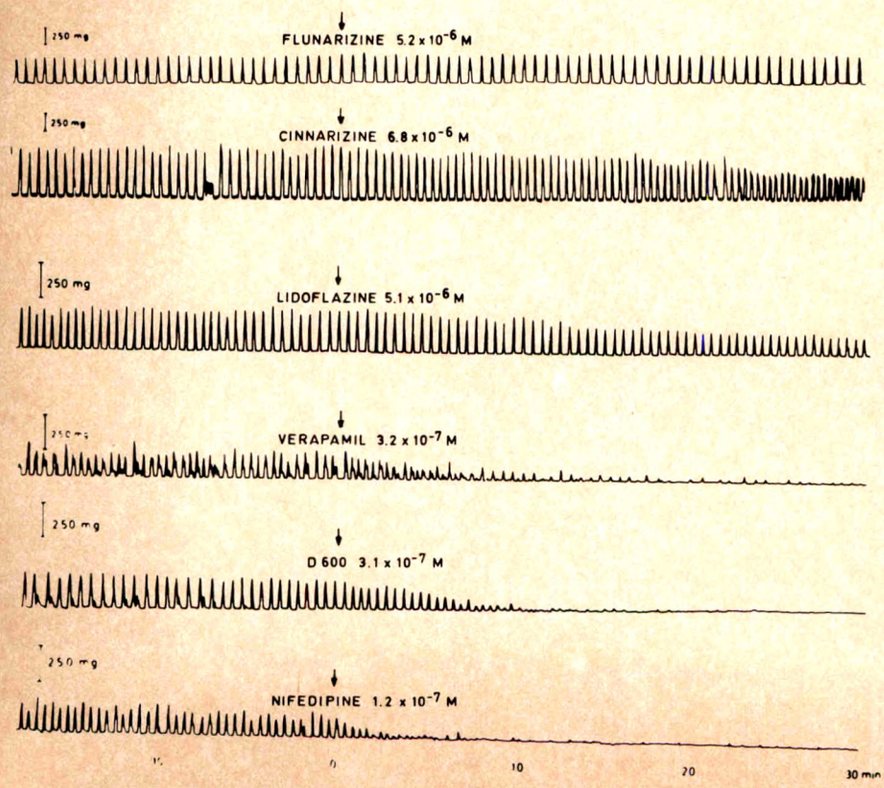


FIGURE 11. Experiments on isolated portal-mesenteric veins of rat. Inhibitory effect of flunarizine, cinnarizine, lidoflazine, verapamil, methoxyverapamil (D 600) and nifedipine on myogenic activity were studied at concentration producing 80 to 100% inhibition of response to Ca^{++} in rat caudal artery preparation. Reprinted with permission from Raven Press.[45]

Acknowledgment: Thanks are due to Janet Beckman for typing the manuscript and to Robert Lorenz for preparing the illustrations.

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Functional Differences in Blood Vessels Determined from Studies with Calcium-Channel Blockers

Functional Changes in Forearm Resistance Vessels of Men With Primary Hypertension

BRIAN F. ROBINSON, MD

Vascular smooth muscle is activated through 2 major systems. One, which can be inhibited by calcium-entry blocking agents, involves the influx of calcium through potential-sensitive channels. The other, which can be inhibited by sodium nitroprusside, involves the entry of calcium through agonist-controlled channels and probably its mobilization from within the cell as well. Human veins, muscular arteries and resistance vessels show differing patterns of response to agents that selectively inhibit the 2 activation systems. The responses indicate that physiologic contractions of cutaneous veins and muscular arteries depend on the agonist-controlled system; contractions of veins induced by high concentrations of potassium depend on the potential-sensitive system as, probably, does local spasm in arteries. The tone of resistance vessels depends on a balance between the potential-sensitive and agonist-controlled systems. The forearm resistance vessels of men with primary hypertension respond to verapamil with larger-than-normal dilatation compared with that induced by nitroprusside. This is interpreted as showing an increased contribution to resistance vessel tone from the potential-sensitive system. This functional abnormality does not depend on the inhibition of sodium pump activity that is known to occur in hypertension, because it cannot be reproduced by local infusion of ouabain. It probably results from a primary disorder of calcium handling by the cell membrane.

(Am J Cardiol 1985;55:24B–29B)

Different types of blood vessels play widely differing roles in circulatory control and it is not surprising that vascular smooth muscle, unlike skeletal or cardiac muscle, shows considerable functional diversity. The varying modes of contractile behavior that it exhibits are associated with a range of mechanisms whereby the concentration of free calcium in the cytosol can be increased and activation of the contractile mechanism achieved. The activation systems are complex and the details of their operation far from clear. This article presents an oversimplified but nonetheless useful framework within which to consider the functional behavior of blood vessels.

From the Department of Medicine, St. George's Hospital Medical School, London, England.

Address for reprints: Brian F. Robinson, MD, FRCP, Department of Pharmacology, St. George's Hospital Medical School, London SW17 ORE, England.

Activation Systems in Vascular Smooth Muscle

There appear to be 2 major systems by which activation of vascular smooth muscle can be achieved.[1] The first involves entry of calcium through potential-sensitive channels in the cell membrane that are analogous to the slow-calcium channels in myocardial cells. This activation system is controlled by membrane potential, but can be modulated by agonists such as noradrenaline. The potential-sensitive channels are selectively inhibited by calcium-entry blockers such as verapamil and nifedipine. The second system is less clearly defined; it appears to involve calcium entry through membrane channels that are agonist-controlled and probably involves release of calcium from intracellular stores. The second system, or group of systems, is relatively insensitive to verapamil and even less sensitive to nifedipine. It is selectively inhibited by sodium nitroprusside and organic nitrates.

The potential-sensitive system is typically involved in spontaneous phasic activity as in the rhythmic contractions of the rat portal vein; such activity is associated with bursts of action potentials that may be triggered by slow oscillations of the membrane potential.[2] The potential-sensitive system also mediates the sustained contractions that develop when the membrane is depolarized by exposure to high concentrations of extracellular potassium.

The agonist-controlled system is typically involved in sustained contractions induced by agents such as noradrenaline; it mediates the tonic contractions of cutaneous veins that result from sympathetic nerve activity. It is also involved in sustained contractions of large arteries whether induced in vivo by sympathetic nerve activity or in vitro by noradrenaline.

Methods for Investigation of Human Blood Vessels

We examined responses to vasoactive agents in 3 different types of blood vessels: the forearm resistance vessels, dorsal hand veins and small collateral arteries that course around the elbow. The response of the forearm vascular bed is dominated by that of the resistance vessels in skeletal muscle: the forearm resistance vessels were assessed by local infusion of drugs into the brachial artery on 1 side and measurement of changes in blood flow by venous occlusion plethysmography using mercury-in-silastic strain gauges. Dorsal hand veins serve as a model for superficial limb veins and their response mirrors that of the systemic venous reservoir as a whole. Drugs are infused locally into a single hand vein, which is congested to a pressure of about 15 mm Hg by a cuff on the upper arm. Changes in vein size are detected by a simple displacement transducer that rests on the vessel about 1 cm below the infusion point.[3] Vessels such as the ulnar collateral, which connect the distal segment of the brachial artery to the proximal parts of the radial and ulnar arteries, serve as models of small muscular arteries. Their responses are assessed by estimating their resistance to blood flow during temporary occlusion of the brachial artery. Resistance is derived from simultaneous measurement of the forearm blood flow and the pressure difference that develops between the brachial and forearm arteries during arterial occlusion. Collateral arterial resistance is measured before and after systemic administration of drugs.[4]

The comparative effectiveness of dilator agents in forearm resistance vessels and dorsal hand veins is assessed by determining the relative potencies of 2 or more drugs, first in 1 type of vessel and then in the other. In the forearm resistance vessels, for example, sodium nitroprusside induces dilatation at about one-tenth the dose required for verapamil; in the hand veins, however, nitroprusside is effective at about one-thousandth the dose of verapamil (Fig. 1). Because blood flow in the brachial artery is likely to be at least 20 times greater than that in a single hand vein, it can be inferred from the dose-response curves that veins are probably somewhat less sensitive to verapamil than resistance vessels; they are, however, much more sensitive to nitroprusside. From such studies, it has been possible to determine the differential responsiveness of resistance vessels and veins to several vasoactive agents; some of these findings are summarized in Table I.

Many dilator drugs act preferentially on blood vessels of 1 type, but the reasons for this selectivity vary. The venoselectivity of the α_1 adrenoceptor antagonist, prazosin, reflects the fact that cutaneous veins depend entirely on sympathetic stimulation for maintenance of contraction; in contrast, resistance vessels possess intrinsic tone and do not relax completely when noradrenergic activity is inhibited. Differential responses to other drugs may reflect differences in innervation or receptors, differences in responsiveness to metabolites and differences in the contribution of mediators arising in the intima. For drugs such as verapamil and nitroprusside, however, differences in response depend on the varying importance of the potential-sensitive and agonist-controlled systems in activating the vascular smooth muscle. From studies of the effects of drugs in

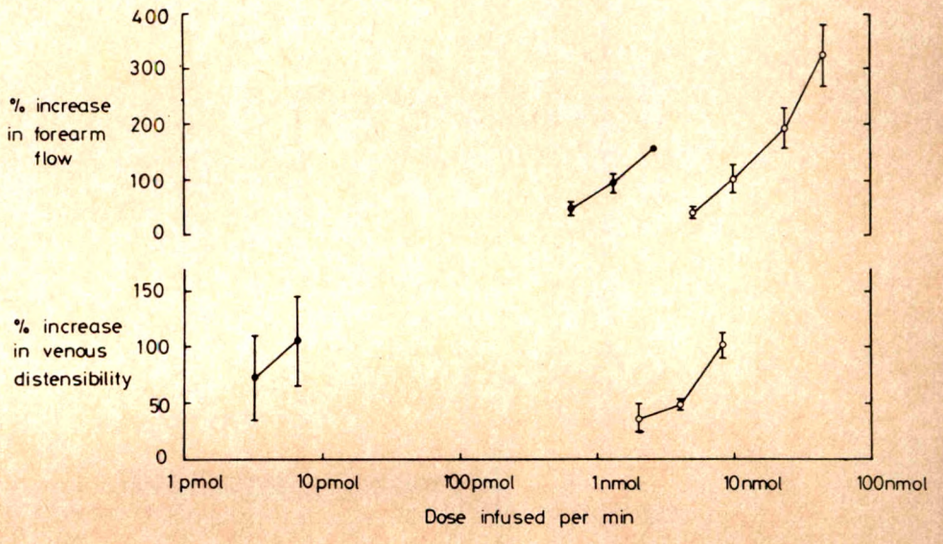

FIGURE 1. Effect of verapamil (**open circles**) and sodium nitroprusside (**closed circles**) on forearm blood flow and distensibility of noradrenaline-constricted hand vein. Mean and standard error of the mean are shown. Dose ratio in forearm is about 10:1; in vein it is 1,000:1. Reprinted with permission from *Cardiovasc Res.*[6]

TABLE I Comparative Effectiveness of Dilator Agents in Blood Vessels of Different Types in Man

Drug	Mechanism of Action	Cutaneous Veins		Muscular Arteries	Resistance Vessels
		Noradrenaline-Contracted	High K^+-Contracted		
Nifedipine	Inhibit calcium entry	0	++	0	++
Verapamil	through potential-sensitive channels	+	++	?	++
Glyceryl trinitrate	Inhibit other systems for calcium entry or release	++	+	++	+
Sodium nitroprusside		++	?	?	+
β-agonists	β adrenoceptor linked-cAMP generation	+	?	+	++
Prazosin	α_1-adrenoceptor antagonist	++	0	?	+
Hydralazine	Not known	0	0	?+	++
Diazoxide	Not known; ? acts on common mechanism at late stage of activation process	+	?	?	+

For references see Robert B, Collier JG. Vascular smooth muscle; correlations between basic properties and responses of human blood vessels. *Br Med Bull* 1979;35:305–312.
cAMP = adenosine 3′:5′-cyclic monophosphate; K^+ = potassium; + = sensitive; ++ very sensitive.

these groups, it has been possible to learn something of the functional differences between blood vessels of different types.

Functional Characteristics of Human Blood Vessels

The independent operation of the potential-sensitive and agonist-controlled systems for activation of smooth muscle can be most clearly observed in the behavior of the dorsal hand veins in man. Physiologic contractions of these vessels, as with other large subcutaneous veins, are normally dependent on stimulation by the sympathetic nerves that supply them. Sustained contractions that mimic those occurring physiologically can be induced by local infusion of noradrenaline in the range of 4 to 32 ng/min. Noradrenaline-induced contractions of this type can be inhibited by low concentrations of sodium nitroprusside, which is consistent with their being mediated by the agonist-controlled system.[5] As would be expected, they are relatively insensitive to verapamil[6] and resistant to nifedipine at concentrations up to 100 times the threshold for relaxation of the resistance vessels.[7] As the noradrenaline-contracted vein is relaxed by nitroprusside, however, small-amplitude phasic contractions with a frequency of 5 to 6 per minute are often seen (Fig. 2). These nitroprusside-resistant contractions are inhibited by relatively low concentrations of verapamil,[6] which is consistent with activation by the potential-sensitive system.

The differential effect of nifedipine on sustained contractions of hand veins evoked by local infusion of noradrenaline and potassium, respectively, provides a particularly clear illustration of the 2 basic modes of activation. Hand vein contractions induced by noradrenaline are unaffected by local infusion of nifedipine in doses up to 3.2 μg/min. When contractions of similar magnitude are produced by local infusion of potassium (K^+), 100 mmol/liter (together with phentolamine to block the effect of released noradrenaline), they can be inhibited by infusion of nifedipine in the range of 100 to 400 ng/min.[7] The noradrenaline-induced contraction depends on the agonist-controlled system; the appar-

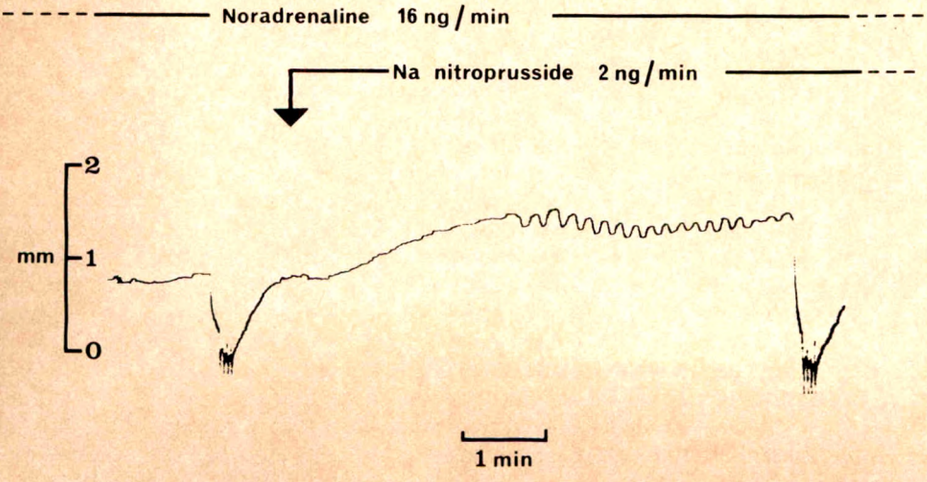

FIGURE 2. Response of noradrenaline-constricted hand vein to sodium nitroprusside: continuous recording of size of single dorsal hand vein maintained at constant pressure by cuff on upper arm inflated to 25 mm Hg. Cuff was deflated on 2 occasions and vein allowed to collapse to establish baseline. Vein was preconstricted by local infusion of noradrenaline at 16 ng/min. Infusion of sodium nitroprusside at 2 ng/min induces relaxation of sustained contraction, but leads to appearance of small-amplitude phasic contractions. Reprinted with permission from *Br J Clin Pharmacol.*[5]

ently similar contraction induced by high concentrations of K^+ results from depolarization with activation of the potential-sensitive system.

Varying patterns of smooth muscle activation may be observed in vessels of other types. Small arteries appear, in general, to behave in a way similar to cutaneous veins with physiologic tone depending on the agonist-controlled system. In accordance with this pattern, the collateral arteries that normally course around the elbow in man were found to decrease their resistance by about half after sublingual administration of glyceryl trinitrate (0.5 mg)[4], but showed no decrease in resistance after 10 mg of sublingual nifedipine.[7] The large coronary arteries may have a slightly different pattern of activation: they dilate readily to both glyceryl trinitrate and nitroprusside.[8] However, some vessels also show partial relaxation in response to intravenous verapamil[9] and a minority were found to dilate weakly in response to sublingual nifedipine.[10] It is interesting to note that localized spasm of coronary arteries is typically very sensitive to nifedipine;[11] this suggests that the pathologic mode of contraction involved in spasm depends on the potential-sensitive system and presumably depends on local depolarization of the vascular smooth muscle. The observation that organic nitrates may also be effective in relieving spasm is not inconsistent with this view because the nitrates can induce partial relaxation of K^+-induced contractions.[12]

Little is known of the behavior of the portal and splanchnic veins in man. In several animal species, however, the portal vein exhibits strong phasic contractions that are selectively inhibited by calcium-entry blockers.[1]

The control of resistance vessels is more complex than in the larger vessels and the relative importance of the 2 basic modes of activation almost certainly differs from bed to bed. In resistance vessels of the human forearm, both potential-sensitive and agonist-controlled systems contribute to the maintenance of tone; neither verapamil nor sodium nitroprusside can induce full dilatation, even at maximally effective doses.[13] These characteristics probably reflect the behavior of the skeletal muscle bed; blood flow in the fingertip skin does not increase in response to verapamil.[14]

Functional Changes in Resistance Vessels in Primary Hypertension

In light of the understanding of vascular smooth muscle function gained by studying the effect of dilator agents in normal blood vessels, it appeared that it should be possible to use drugs of this type to investigate functional changes occurring in circulatory disorders. The relative effectiveness of a calcium-entry blocking drug and of sodium nitroprusside in inducing dilatation of the same resistance bed should provide an indication of the relative importance of the 2 activation systems in maintaining vascular tone. We decided to use this approach to investigate the functional behavior of forearm resistance vessels in patients with hypertension.

A functional disorder in the resistance vessels has long been considered as a possible mechanism by which an increase in arterial pressure might be initiated and maintained. Several studies demonstrated an enhanced response to noradrenaline,[15–17] but it has been pointed out that this could result entirely from structural changes in the vessels and need not imply any functional change in the vascular smooth muscle.[18] It is known that long-term increase of arterial pressure leads to medial hypertrophy with an increase in the wall lumen ratio in the arterioles.[19] It has been reasoned from this that as the smooth muscle of the media contracts, the thickened media will encroach on the lumen. The result is that for any given fractional shortening of the myocytes, a greater-than-normal increase in vascular resistance occurs. Thus it has been proposed that the effects of both constrictor and dilator agents on vascular resistance may be enhanced in patients with hypertension purely as a result of structural changes in the vessels.[18] Any attempt to demonstrate a functional abnormality in the resistance vessels must overcome this argument.

An initial study of the effect of dilator agents on forearm resistance vessels was carried out in 35 men with primary hypertension and 23 men with normal arterial pressures of similar age range.[20] Forearm blood flow was measured by venous occlusion plethysmography with mercury-in-silastic gauges. Drugs were infused into the brachial artery on 1 side and dose-response curves were obtained to increasing doses, first of verapamil and then, after an appropriate interval, sodium nitroprusside. The patients had a significant enhancement of the dilator response to verapamil; their response to nitroprusside, however, tended to be less than that of the normal control subjects. When the response to verapamil was compared with the response to nitroprusside in the same subjects, the patients had a highly significant enhancement of the response to verapamil relative to nitroprusside (Fig. 3). A similar increase in responsiveness to verapamil was reported from Switzerland.[13] The difference in response to the 2 dilators cannot be explained by structural changes in the vessels because if these had influenced the decrease in resistance that was achieved, they would have increased the response to both drugs to a similar extent. As with other nonspecific influences, the effect would have been to shift response to the upper part of the normal regression line (Fig. 3). The alteration in responsiveness must therefore reflect a functional disorder. We believe these findings show that the potential-sensitive system makes a proportionally greater contribution to the maintenance of resistance vessel tone in patients with hypertension than in normal subjects. This agrees with the view that the increase in vascular resistance results from a selective increase in the intrinsic, or myogenic, component of arteriolar tone because this is believed to depend on the entry of calcium through potential-sensitive channels.

There is evidence of impaired sodium pump activity in the leukocytes of patients with hypertension and it is believed that this results from the presence of circulating inhibitor in plasma.[21] It has been proposed that

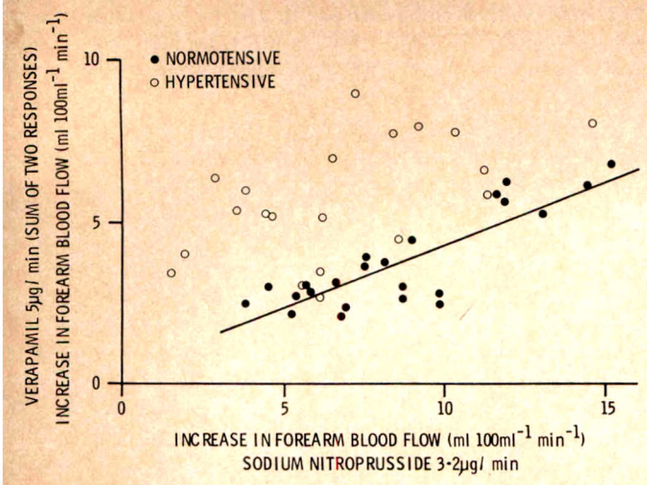

FIGURE 3. Increase in forearm blood flow in response to sodium nitroprusside (3.2 μg/min) related to sum of responses to 2 infusions of verapamil (5 μg/min). Responses to 2 drugs vary widely in normotensive subjects (**closed circles**), but show close linear correlation ($r = 0.85$, $p < 0.01$); this indicates that variability results from nonspecific factors that influence response to both dilators. Most patients with hypertension (**open circles**) have responses to verapamil that exceed those expected from response to nitroprusside. Reprinted with permission from *Clin Sci.*[20]

pump activity is also depressed in the smooth muscle of the resistance vessels with a consequent increase in intracellular sodium. It has been further proposed that increased intracellular sodium reduces the effectiveness of a sodium/calcium exchange mechanism, and so leads to an increase in cytosolic calcium with a resultant increase in resistance vessel tone[22,23] We therefore attempted to determine if the enhanced responsiveness to verapamil in patients with hypertension was a consequence of decreased sodium pump activity. Ouabain was infused into the brachial artery of normal subjects at 2 μg/min for 1 hour. This procedure impaired the dilator response to small increments in plasma K^+ concentration, indicating that significant inhibition of sodium pump activity had been achieved, but it had no effect on the response to verapamil or nitroprusside.[24] We concluded that the enhanced activity of the potential-sensitive activation system did not result from decreased activity of the sodium pump.

In more recent studies, it has been shown that responsiveness to verapamil can be selectively altered by small changes in plasma calcium concentration. Infusion of calcium into the brachial artery at a rate sufficient to increase the plasma concentration by about 0.5 mmol/liter depresses the response to verapamil in both normal subjects and patients with hypertension.[25,26] After discontinuing calcium infusion, responsiveness to verapamil increases in the resistance vessels of normal subjects so that their pattern of response now resembles that of patients with hypertension.[25] It thus appears that the activity of the potential-sensitive system can be modulated by calcium itself. Depression of activity during calcium infusion is probably mediated by an increase in calcium binding to the membrane. The increase in activity when the infusion is discontinued must reflect the induction of some long-lasting change in the physico-chemical characteristics of the membrane, but the nature and mechanism of this transformation are unknown.

A growing body of evidence points to an underlying abnormality in the way in which calcium is handled by cell membranes in hypertension: adenosine triphosphate-dependent calcium transport is impaired in membrane preparations derived from vascular smooth muscle of the spontaneously hypertensive rat,[27,28] and calcium binding appears defective in erythrocytes from both the rat[29] and patients with primary hypertension.[30] Calcium plays an important role in regulating membrane function that is distinct from its direct role in activating the contractile mechanism: by binding to sites on the membrane, calcium ions are able to inactivate certain potential-sensitive channels and can thus inhibit their own entry into the cell.[31,32] The results of our studies of resistance vessel function, taken in conjunction with the work of others on membrane function, are thus consistent with the view that a calcium-binding disorder accounts for the increased activity of the potential-sensitive system in primary hypertension. A disorder of this type, which could well be genetic in origin, may be an important factor in the development and maintenance of increased peripheral resistance. Thus insights into the mechanism of vascular smooth muscle contraction gained from the use of calcium-entry blockers are proving of major assistance in furthering understanding of the nature of the functional changes in the resistance vessels in primary hypertension.

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Pharmacokinetics of Calcium-Entry Blockers

R. G. McALLISTER, Jr., MD, SCOTT R. HAMANN, PhD, and ROBERT A. BLOUIN, PharmD

Effective use of drugs in therapy depends not only on clinical acumen but also on the availability of relevant pharmacokinetic and pharmacodynamic data. Such information assists in development of safe dosing regimens, prediction of abnormal handling of drugs in states of disease and disorder and anticipation of drug interactions. For the calcium-entry blocking agents now available in the United States (verapamil, nifedipine and diltiazem), these data appeared well after clinical patterns of use evolved. Nonetheless, their relevance continues to be demonstrated by the dependence of each agent on intact liver blood flow and function for normal rates of elimination; by the nonlinear kinetic characteristics for verapamil and diltiazem (and probably for nifedipine, as well) and the derivative implications for decreased dosing frequency requirements; and by observations now appearing on the relation between plasma drug levels and drug effects, both therapeutic and toxic. Such data are discussed herein, with emphasis on those aspects that impact on the clinical use of the calcium-entry antagonists.

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The clinically relevant pharmacokinetic characteristics of any drug may have profound implications at the bedside. The term "pharmacokinetics" incorporates both demonstrated facts and inferred assumptions about a drug's absorption, distribution, metabolism and elimination in patients. Furthermore, the relation between the intensity and duration of therapeutic and toxic actions of a drug is inherent in pharmacokinetic profiles. Such information must be available to support the development of rational dosing regimens, to anticipate the probability of interactions with other therapeutic agents and to predict deviations from expected patterns in drug handling by patients with various disorders. Good medical practice is clearly dependent on an understanding of the pharmacokinetic characteristics of drugs prescribed.

The clinician frequently incorporates pharmacokinetic principles[1–3] into his or her use of therapeutic agents but infrequently recognizes this intuitive approach. We will briefly review selected aspects of kinetics that fall into this category and that may serve as a basis for subsequent consideration of the kinetic characteristics of specific calcium-entry blocking agents.

Drug absorption after oral administration may vary because of the characteristics of the chemical drug substance or its formulation. After intravenous administration, all the drug given is available for distribution to target tissues. The ratio of the amount of drug available to sites of action after an oral dose to that available after intravenous administration is called the bioavailability of a drug (usually labelled as F and reported as a percentage of the intravenous dose). Although the absorption process itself may limit bioavailability, the role of the liver in extracting absorbed drug from the portal circulation is generally more important. This "first-pass" effect may vary substantially among subjects and may account for wide variation in doses of specific drugs required for desired effects in different persons. For drugs not subject to hepatic metabolism, first-pass extraction is not a major consideration.

Drug distribution from the central compartment (such as circulating blood) to peripheral tissues occurs at variable rates, which will determine the time required to accumulate drug at sites of action to the critical concentrations required for therapeutic effects. This is a dynamic process, with elimination beginning even as distribution proceeds. The rate and extent of a drug's distribution to target tissues may vary substantially with systemic versus oral dosing,[4] resulting in differences in observed effects between the 2 dosing routes

From the Research Service, Veterans Administration Medical Center; the Departments of Medicine and Pharmacology, the Graduate Center for Toxicology, and the College of Pharmacy, the University of Kentucky College of Medicine, Lexington, Kentucky. This study was supported in part by funds from the Veterans Administration, Washington, D.C.

Address for reprints: R. G. McAllister, Jr., MD, FACC, ACOS/R&D (151-CDD), Veterans Administration Medical Center, Lexington, Kentucky 40511.

TABLE I Verapamil Pharmacokinetics—Normal Subjects

Dose (mg, route)	T/2$^{\beta}$ (hours)	Vd (area) (liter)	Clearance (ml/min)	F (%)
McAllister and Kirsten[11]				
10, IV	4.8 ± 2.4	347 ± 184	847 ± 370	. . .
80, PO	4.5 ± 2.4	406 ± 310	4,831 ± 2,030	18 ± 10
160, PO	4.8 ± 3.8	399 ± 325	4,307 ± 2,059	20 ± 12
Eichelbaum et al[29]				
10, IV	3.7	418 ± 109	1,258 ± 193	. . .
80, PO	3.5	. . .	6,383 ± 2,320	22 ± 8

F (%) = bioavailability; IV = intravenous; PO = orally; T/2$^{\beta}$ = elimination half-life; Vd (area) = apparent volume of distribution estimated from the area under the plasma concentration versus time curve.

that cannot be attributed to absorption or first-pass extraction variables.

Drug elimination from the body may more often be considered as a first-order process, in which the rate of elimination is directly proportional to the concentration of the drug remaining in the body. The kinetic characteristics of the calcium-entry blocking agents studied thus far are consistent with first-order disposition. In the presence of this type of nonsaturated elimination, the *rate* of drug elimination can be described by mono- or poly-exponential equations derived from serial measurements, after dosing, of drug concentrations in blood versus time. From the slope of the terminal linear phase of such data plotted in semilogarithmic fashion may be derived a rate constant for elimination, which itself is used to calculate a more familiar term, *the drug half-life*—the time required for drug levels in blood (or plasma) to decrease by 50%.

Another useful concept is *clearance*, which is defined as the volume of blood (or plasma) cleared of drug per unit time. If a specific drug is subject to clearance by the liver, for example, and its clearance is dependent on its rate of delivery to the liver, the drug's rate of elimination will depend upon liver blood flow (that is, flow-dependent clearance). In clinical conditions in which liver blood flow is altered, as in portal hypertension, the clearance will be significantly changed, with the attendant implications of drug accumulation and potential toxicity. Alterations in drug clearance affect drug half-life in reciprocal fashion; as clearance increases, half-life decreases.

During *long-term drug administration*, whether by continuous intravenous infusion or repeated oral doses, accumulation to steady-state or plateau concentrations may be predicted from the half-life: over 1 half-life unit, 50% of steady-state concentrations will be achieved, and over 5 half-life units, 97% of plateau levels will be present. When a drug has a long half-life, loading doses may be required to achieve rapid blood/tissue concentrations in the therapeutic range. Only recently has the nonlinear accumulation of drugs been widely recognized; in this circumstance, drug accumulation well beyond that predicted from the "5 × half-life" rule may be seen. This phenomenon may result from changes in the pharmacokinetic characteristics of a drug deriving from its own hemodynamic or metabolic effects. For example, the profound vascular actions of the calcium-entry blocking agents may actually reduce liver blood flow by dilating other regional vascular beds, thereby reducing the hepatic clearance of the drugs themselves. The pharmacokinetic profiles for drugs with significant hemodynamic actions may differ during long-term dosing from the profiles seen after single-dose studies. Therefore, predictions derived from single-dose kinetics must be viewed as approximations until confirmed by evaluations carried out during long-term drug administration.

As each of these variables is considered singly and in combination with others, the underlying assumption is that the concentration of the drug at specific sites of action is directly related to the effects observed, whether therapeutic or toxic, and, further, that the levels of drug at these tissue sites are related, loosely or intimately, to concentrations measured in blood. This principle of *pharmacodynamics* may be particularly useful in consideration of the calcium-entry blocking drugs, because they have, as a group, profound hemodynamic or electrophysiologic effects or both, and concomitant potential for therapeutic and toxic activity.

Verapamil

Although verapamil was introduced approximately 20 years ago in Germany, detailed descriptions of its pharmacokinetic characteristics did not become available until the late 1970s because of slow development of analytical methods capable of measuring concentrations of the drug in plasma with requisite sensitivity and specificity. At the present time, both high pressure liquid chromatographic and gas chromatographic techniques can be used to measure levels of the parent drug and its major metabolites.[5–10]

The pharmacokinetics of verapamil in normal subjects after single intravenous and oral doses are listed in Table I and Figures 1 and 2. Interestingly, the half-life after intravenous administration is similar to that seen after oral drug administration.[11] During long-term oral administration, nonlinear accumulation of the drug occurs, with reduced clearance and prolongation of the half-life value.[12,13] This latter observation has clinical importance: it implies that verapamil in its current oral formulation may be administered on a twice-daily schedule after accumulation to steady state has occurred, although most clinical studies have used regimens requiring 3 or 4 doses per day.

Verapamil is eliminated exclusively by the liver;[14] metabolism is effected by a cytochrome P450 system, in which Michaelis-Menten kinetics are demonstrable[15] (Fig. 3) and for which phenobarbital induction and SKF

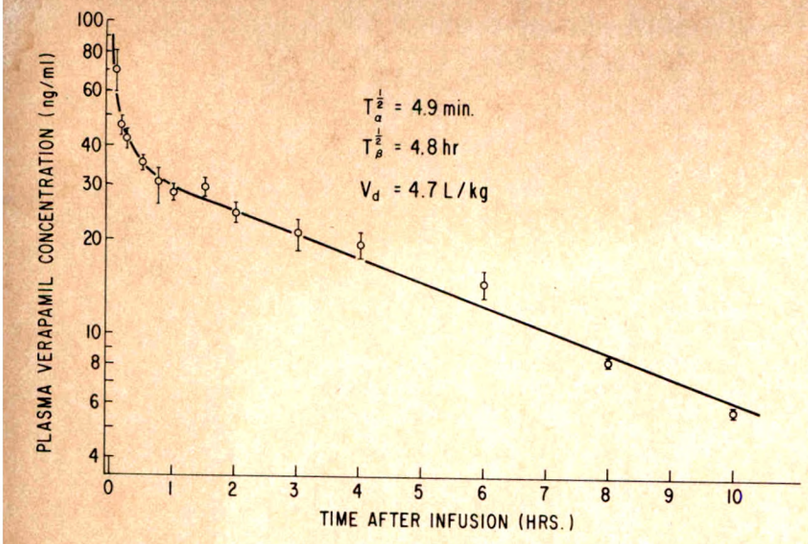

FIGURE 1. Pharmacokinetic profile of verapamil, 10 mg intravenously, in 28 normal subjects (data from McAllister et al[11]).

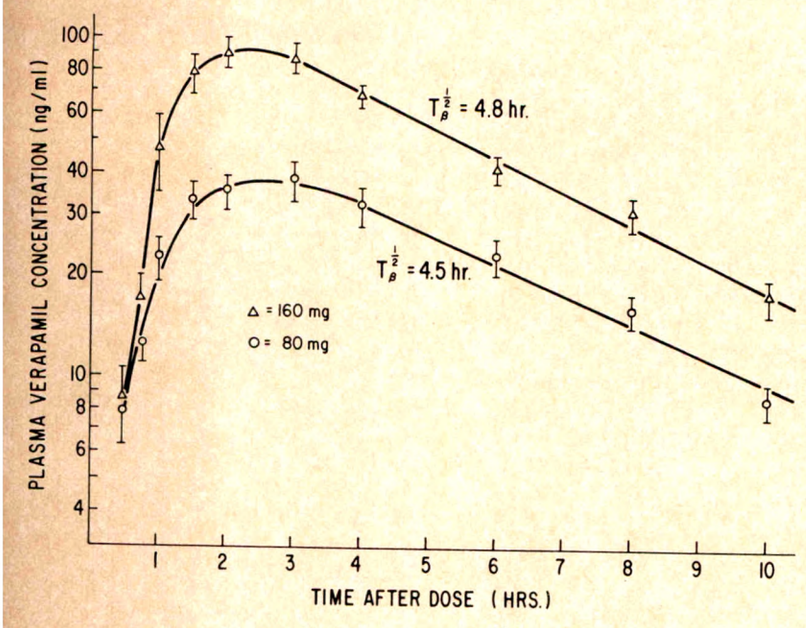

FIGURE 2. Pharmacokinetic profile of verapamil after single oral doses in 20 normal subjects (data from McAllister et al[11]).

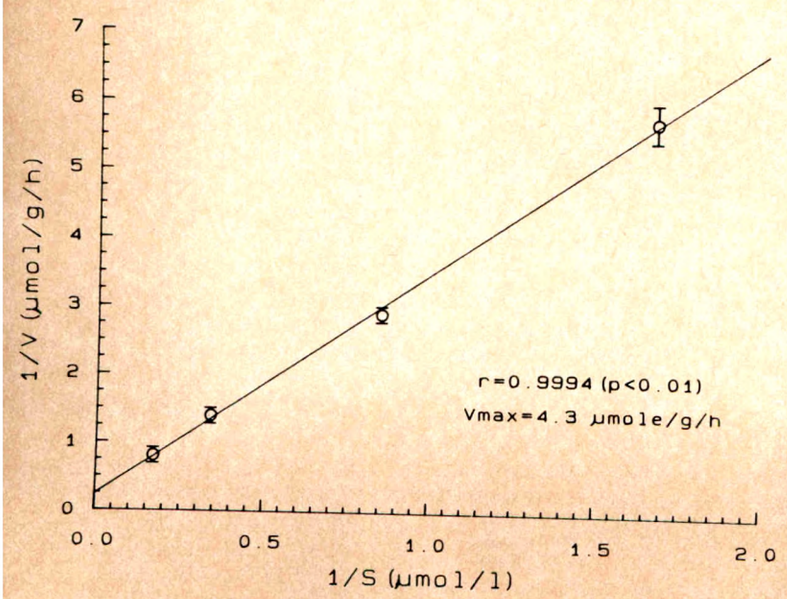

FIGURE 3. Metabolism of verapamil by rat liver microsomes, shown in Lineweaver-Burk format. No saturation is evident at higher concentrations. S = substrate concentration; V = rate of metabolism.

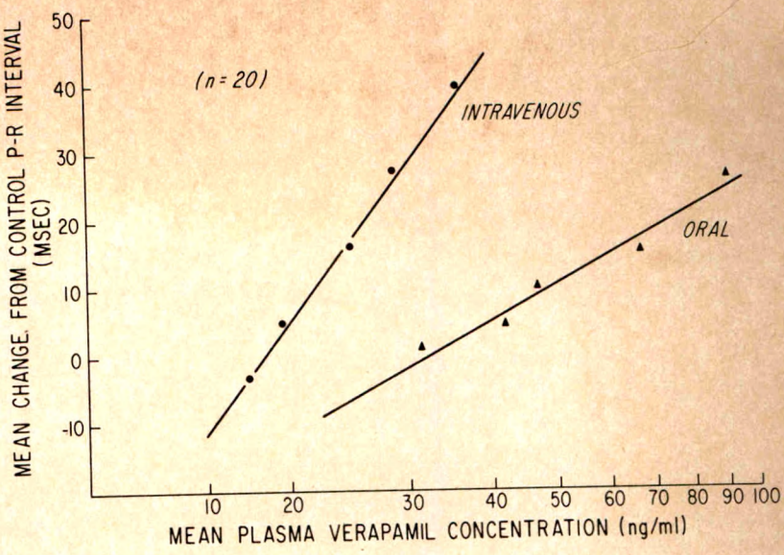

FIGURE 4. Plasma verapamil concentration versus mean change in P-R interval from control, after 10-mg intravenous and 80-mg single oral doses, in 20 normal subjects. Note differences in slopes and position of plasma level-effect lines (data from McAllister et al[11]).

525A suppression have been demonstrated.[16] Of the various metabolites,[17] only the N-demethylated form (norverapamil) has significant activity, which is only about 20% of the parent drug in studies with coronary vascular strips *in vitro*.[18] In the presence of normal liver function, oral verapamil is subject to extensive first-pass extraction, such that oral bioavailability is only about 20% (Table I). In patients with hepatic cirrhosis, first-pass effects are diminished, clearance decreased and bioavailability enhanced; drug accumulation to toxic levels may occur in such patients during administration of conventional doses.[19] In patients with chronic atrial fibrillation, higher bioavailability (35%) and longer half-life values (6 to 8 hours) were reported by Kates et al;[20] Anderson et al,[21] in a similar patient group, found half-life values similar to those in normal subjects but reduced bioavailability and clearance. It is possible that the presence of arrhythmia in these 2 study groups contributed to relative decreases in cardiac output and liver blood flow, thereby decreasing drug clearance. Further kinetic studies in patient groups are clearly desirable.

Verapamil has been reported to be highly bound to plasma proteins,[22] including both albumin and α-1 acid glycoprotein.[23] The latter protein appears to be largely responsible for binding variability seen in patients with supraventricular tachycardias. Verapamil can be displaced from binding sites in vitro by lidocaine, diazepam, propranolol and disopyramide.[24] These observations have not yet been validated by in vivo studies, and no clinically important drug interactions deriving from binding-site displacement of verapamil have been reported.

The plasma level-effect relations for verapamil are complex. After intravenous drug administration, a linear relation between drug levels and effects on atrioventricular conduction can be seen[11,25] (Fig. 4); at plasma levels <250 ng/ml, vasodilation occurs and cardiac output increases, but above this level, negative inotropic effects become evident and cardiac output decreases progressively[26] (Fig. 5). The electrophysiologic effects of verapamil occur preferentially, with the result that atrioventricular block is likely to occur before substantial hemodynamic toxicity is manifest.[26,27] (Fig. 6). When basal left ventricular pump function is significantly impaired, negative inotropic effects of verapamil are manifest at lower drug plasma levels.[28] After oral drug administration, plasma concentrations of verapamil required for specific effects on atrioventricular conduction are 2- to 3-fold higher than after intravenous dosing[11,25] (Fig. 4). Eichelbaum et al[29] suggested that this is due to preferential first-pass extraction of the relatively more active L-isomer of verapamil, whereas Hamann et al[4] reported data suggesting that tissue distribution patterns of verapamil

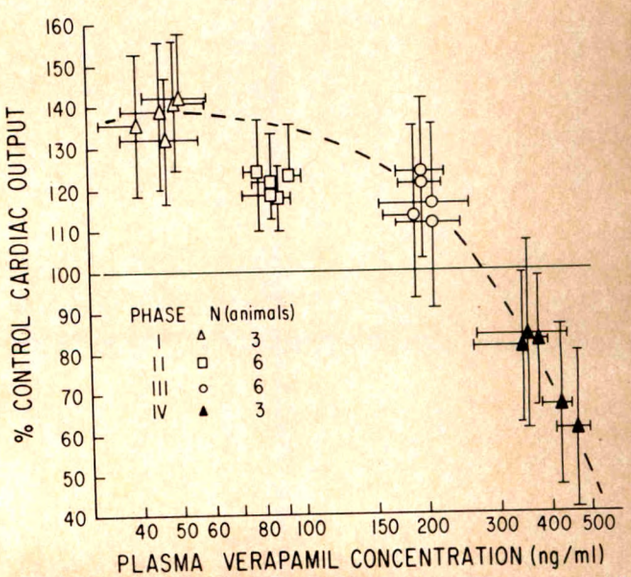

FIGURE 5. Correlation between plasma concentrations of verapamil during constant intravenous infusions and percent change in cardiac output from control levels, in mongrel dogs anesthetized with pentobarbital. Data points reflect means of observations made at 20, 30, 40, 50 and 60 minutes after beginning verapamil administration. At levels of about 250 ng/ml, direct negative inotropic effects of verapamil begin to become apparent.

TABLE II Nifedipine Pharmacokinetics

Dose (mg)	Tmax (hours)	Cmax (ng/ml)	$T/2^{\beta}$ (hours)	Clearance (ml/min)	F (%)	Reference
Intravenous						
1.0	0.08 ± 0.03	25.9 ± 4.8	1.77 ± 0.25	759 ± 110	. . .	Foster et al[36]
1.0	. . .	. . .	1.26 ± 0.55	550 ± 118	. . .	Raemsch and Sommer[35]
Oral						
(Capsule)						
10	0.57 ± 0.06	73.5 ± 17.5	3.4 ± 10.4	600 ± 110	45 ± 9	Foster et al[36]
10	c. 0.50	153	c. 2.5	. . .	62 ± 7	Raemsch and Sommer[35]
(Tablet)						
20	1.63 ± 0.26	62.6 ± 9.0	10.8 ± 2.4	553 ± 121	. . .	Banzet et al[37]
40	2.13 ± 0.29	109.3 ± 17	10.2 ± 1.8	561 ± 162	. . .	Banzet et al[37]
60	1.75 ± 0.16	170.1 ± 24.3	9.7 ± 1.0	580 ± 136	. . .	Banzet et al[37]

c. = approximate (calculated from data in report); Cmax = peak plasma nifedipine concentration; Tmax = time to peak plasma concentration. Other abbreviations as in Table I.

differ after intravenous as opposed to oral dosing routes and, thus, intensity of drug effects may vary. In addition, the plasma concentration-response relation for verapamil is also significantly affected by variations in sympathetic tone,[11] resulting in wide differences in the plasma drug levels at which specific drug effects occur in different subjects.

Owing, in part, to verapamil's high first-pass extraction, concentrations of verapamil in plasma after administration of the same oral dose to different subjects vary by more than a 10-fold factor (Fig. 7). This observation alone makes the measurement of plasma concentrations of verapamil primarily of research interest and of little clinical importance except to demonstrate noncompliance or abnormal drug handling.

A sustained-release preparation of verapamil was evaluated by Follath et al,[30] who found stable plasma drug concentrations throughout 12-hour dosing intervals. In view of the demonstrated accumulation with conventional verapamil tablets, and the observed prolongation in half-life, the pharmacokinetic rationale for a sustained-release preparation of this drug is obscure.

Further aspects of the pharmacokinetic and pharmacodynamic profiles for verapamil have been reviewed recently.[31–33]

Nifedipine

Nifedipine is a dihydropyridine compound that is eliminated by hepatic metabolism.[34] Metabolism conforms to Michaelis-Menton kinetics (that is, the rate of metabolic elimination is related to the concentration of drug present) in isolated liver homogenate systems (Fig. 8); studies from our laboratory indicate that induction and suppression of metabolism do not occur as they do with verapamil.[16] All metabolites identified are dehydrogenated and pharmacologically inactive.[35] The drug is reported to be 90% bound to plasma proteins.[34]

The pharmacokinetic characteristics of nifedipine are only now being analyzed and reported in detail[35–38] because of early difficulties in development of sensitive and specific assay techniques. Early studies with nifedipine used a fluorimetric procedure, which may measure metabolites as well as unchanged drug.[39]

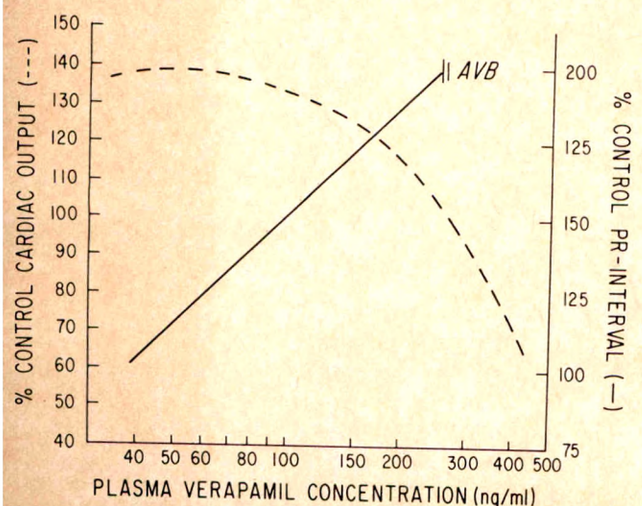

FIGURE 6. In same animals from which data were shown in Figure 5, data from cardiac output and P-R interval changes from control are combined. At plasma drug concentrations (during intravenous infusions to steady-state drug levels) >250 ng/ml, complete atrioventricular block was present and cardiac output depression was approximately at control levels, indicating preferential effects of verapamil on cardiac conduction system.

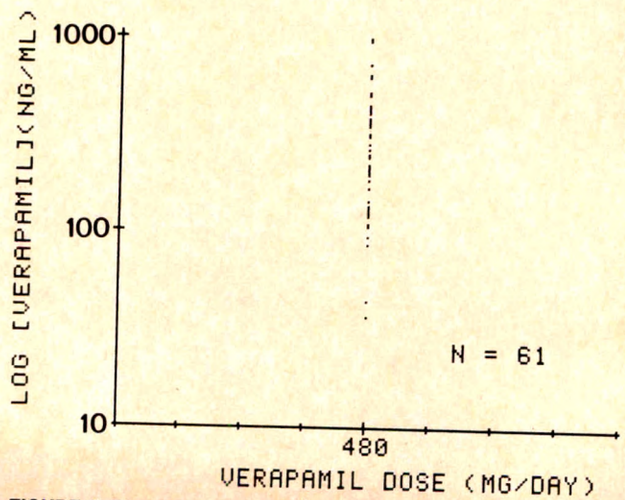

FIGURE 7. Plasma verapamil concentrations 2 hours after dosing in 18 men treated chronically with 480 mg/day of verapamil; 61 plasma samples were analyzed. Each point represents 1 plasma level determination. Scatter among subjects is more than 10-fold.

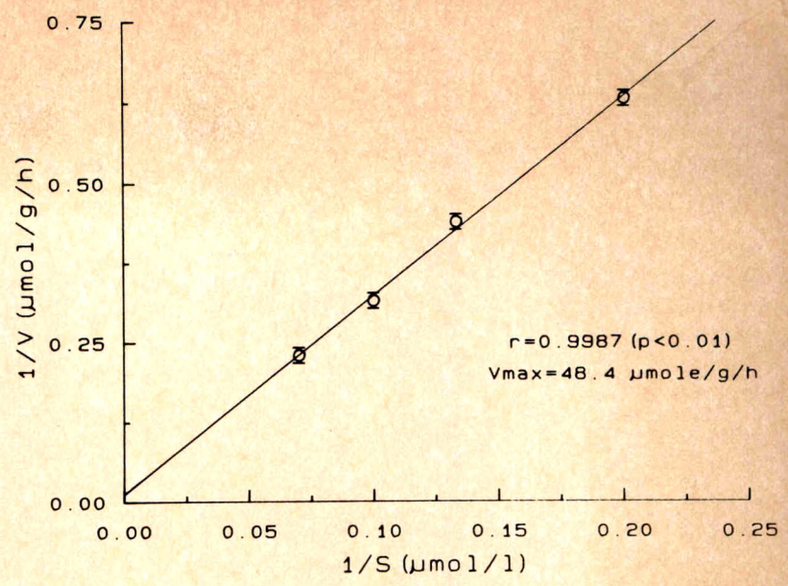

FIGURE 8. Metabolism of nifedipine by rat liver microsomes, shown in Lineweaver-Burk format. No saturation was seen, even at higher concentrations. S = substrate concentration; V = rate of metabolism.

Subsequent work used mass spectrometry,[40] gas chromatography with electron-capture detection,[41–43] and high pressure liquid chromatography.[44] Nifedipine is light-sensitive and rapidly decomposes in solvent when exposed to ordinary light sources; in plasma, however, it appears to be stable for up to 1 hour.[42] It has been suggested that various metabolite forms found in different studies[41] were artifacts from breakdown of nifedipine in solution.[35]

Pharmacokinetic profiles for nifedipine after intravenous administration were reported by Raemsch and Sommer[35] and by Foster et al[36]; both studies were done in normal subjects and used equivalent doses of nifedipine. The results were similar and are shown in Table II. Studies with 2- and 3-mg intravenous doses were performed in our laboratories (Foster et al, unpublished observations); analysis is difficult and requires model-independent approaches, as previously noted by others,[35] because of variation among subjects. Examples of plasma level versus time plots for intravenous nifedipine dosing are shown in Figures 9 and 10. Although these are preliminary results, elimination half-life appears to be prolonged at the 3-mg intravenous dose compared with 1-mg dose, and clearance is decreased. In a study with anesthetized dogs given intravenous nifedipine, we found that clearance was linearly related to liver plasma flow (Fig. 11) (an observation consistent with flow-limited clearance characteristics) and, further, that both clearance and hepatic plasma flow were inversely related to steady-state plasma drug concentrations. The difficulty in analyzing the pharmacokinetics of this drug when higher plasma levels are produced may relate in part to a nonlinear kinetic profile. Further studies are needed to confirm this in patients.

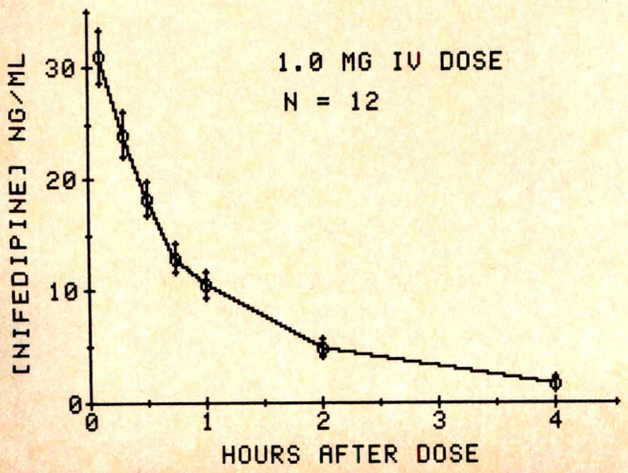

FIGURE 9. Plasma concentrations of nifedipine after intravenous administration of 1 mg to 12 normal volunteer subjects (data from Foster et al[36]).

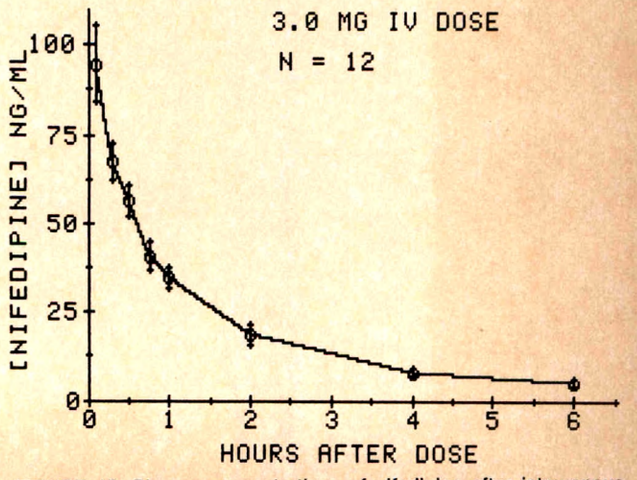

FIGURE 10. Plasma concentrations of nifedipine after intravenous administration of 3 mg to 12 normal volunteer subjects; note that peak plasma levels were 3 times higher than seen with 1 mg doses (Fig. 9). Dosing was carried out under gold fluorescent light to prevent photodegradation of nifedipine.

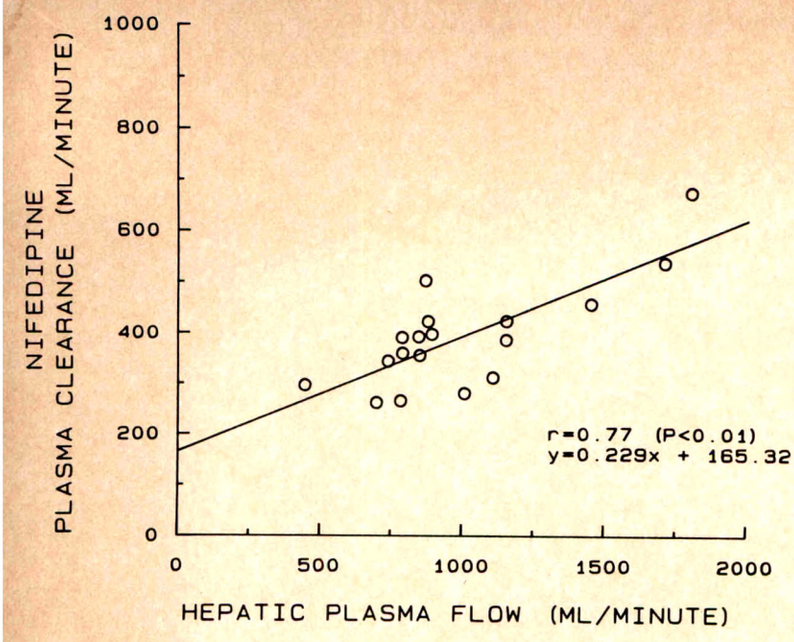

FIGURE 11. Nifedipine plasma clearance versus hepatic blood flow in dogs during pentothal anesthesia. Nifedipine was given intravenously in single doses. These data suggest that nifedipine clearance is, like that of verapamil, a function of hepatic blood flow.

Nifedipine is available in both a liquid-filled capsule and a tablet formulation; only the former is marketed in the United States, although both are available in other countries. The 2 preparations have distinctly different pharmacokinetic properties. Studies in normal subjects given the capsule (10 mg) were reported[35,36] and results are listed in Table II. With the capsule formulation, peak plasma drug levels occurred about 30 minutes after dosing, and elimination half-life values were about double those found with single intravenous doses. Calculated bioavailability ranged from 45% in the study by Foster et al[36] to 62% in the report from Raemsch and Sommer.[35] Wide variation among subjects was found in the former study; 4 of 12 study subjects had a kinetic profile suggesting delayed drug absorption, with peak plasma levels found 4 hours after dosing, which reached only about 25% of the peaks found in the other subjects.

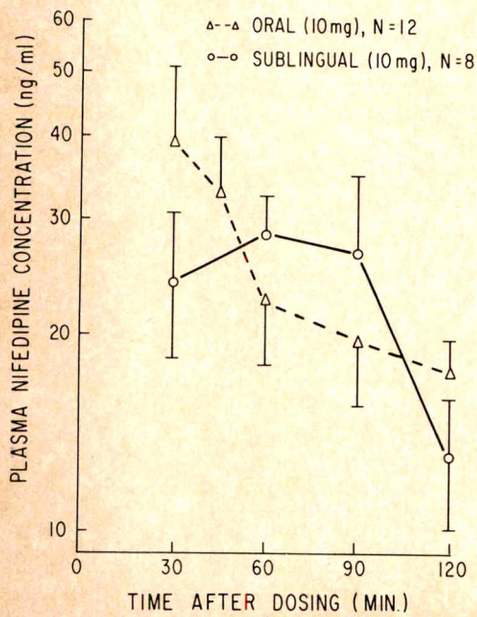

FIGURE 12. Comparison of plasma nifedipine levels after oral administration of single 10-mg capsule (in 12 normal subjects) and sublingual dosing with same preparation (in 8 normal subjects). (Oral data from Foster et al.[36]) Sublingual values were obtained in different but comparable study population. Plasma drug levels after sublingual dosing reach significantly lower peak values, at a later time, than are seen with oral capsule ingestion.

Sublingual administration of the 10-mg capsule was noted by Raemsch and Sommer[35] to produce plasma level peaks lower than those seen after equivalent oral doses; studies from our laboratories have confirmed this in various groups of subjects (Fig. 12). Although sublingual drug administration is widely thought to produce drug effects more rapidly and to a greater intensity than oral administration, current data with the capsule formulation indicate that, in fact, the opposite is often true.

Results from pharmacokinetic evaluation of hypertensive patients[37,38] given nifedipine in tablet form are also listed in Table II. The time to peak plasma levels after the tablet was given is about 3 times that seen with the capsule, and the half-life is 4-fold lengthened. In tablet form, therefore, twice-daily nifedipine dosing is appropriate, whereas the capsule must be given more frequently. Accumulation apparently does not occur with frequently used doses of nifedipine.[35]

Plasma level-effect relation for nifedipine are not as yet well established. In studies with dogs given intravenous nifedipine by infusion, Hamann and McAllister[45] found linear relations between hemodynamic effects (decreases in arterial pressure, increases in cardiac output [Fig. 13]) over a wide plasma level range; no electrocardiographic changes were seen. In hypertensive patients, using the tablet preparation, Taburet[38] reported a significant correlation between plasma concentrations of nifedipine and observed decreases in supine mean arterial pressure, over a range of drug levels

TABLE III Diltiazem Pharmacokinetics[54]

Dose (mg)	Tmax (hours)	Cmax (ng/ml)	$T/2^{\beta}$ (hours)	Clearance (ml/min)	F (%)
Intravenous					
20	Immediately	331.4 ± 116	4.45 ± 1.26	916	. . .
Oral					
First dose					
60–90	a) 1.8 ± 0.5*	63.0 ± 34	3.74 ± 0.57	2475	38 ± 11
	b) 4.7 ± 0.7*	64.7 ± 39			
Sixteenth dose					
60–90	a) 1.6 ± 0.6*	205 ± 80	4.9 ± 0.4	1028	90 ± 21
	b) 4.0 ± 1.0*	192 ± 79			

* Dual plasma level peaks seen after oral dosing.
Abbreviations as in Tables I and II.

from 10 to 250 ng/ml. Although Aoki et al[46] found a similar, if less significant, correlation, Pedersen et al[47]—using nifedipine capsules—found none. These differences may lie in the analytical methods used to measure drug plasma concentrations, the various nifedipine formulations given to the patient subjects, the plasma levels of drug achieved and sustained in different patients or some combination of these factors.

Diltiazem

Diltiazem is a benzothiazepine derivative initially evaluated in Japan.[48] Studies in dogs revealed virtually complete drug absorption after oral administration, with a high first-pass effect[49]; bioavailability of the commercial tablet preparation was 24%.[50] In various species studied, diltiazem was subject to extensive hepatic metabolism, with the major elimination pathway involving deacetylation.[49,50]

With the development of sensitive and specific assay methods for diltiazem estimation in plasma,[51,52] clinically relevant data in patients have rapidly become available. In an early study with orally administered diltiazem, Kinney et al[53] reported that single doses of 30 mg produced plasma drug levels barely measurable; 60, 90 and 120-mg doses resulted in progressively larger areas under the plasma drug level versus time curve. There was a slight prolongation in half-life values as doses increased.

In 8 normal subjects, Smith et al[54] studied the pharmacokinetic properties of diltiazem after intravenous infusions, single oral doses and repeated oral administration (Table III). Triexponential elimination kinetics were observed after both systemic and oral drug administration, and the terminal half-life values were similar with each study protocol (3.7 to 4.5 hours). During long-term oral drug dosing, accumulation of both the unchanged diltiazem and the deacetylated metabolite was observed. Evidence of enterohepatic recirculation was deduced from double peaks often seen in plasma concentration versus time curves. Of partic-

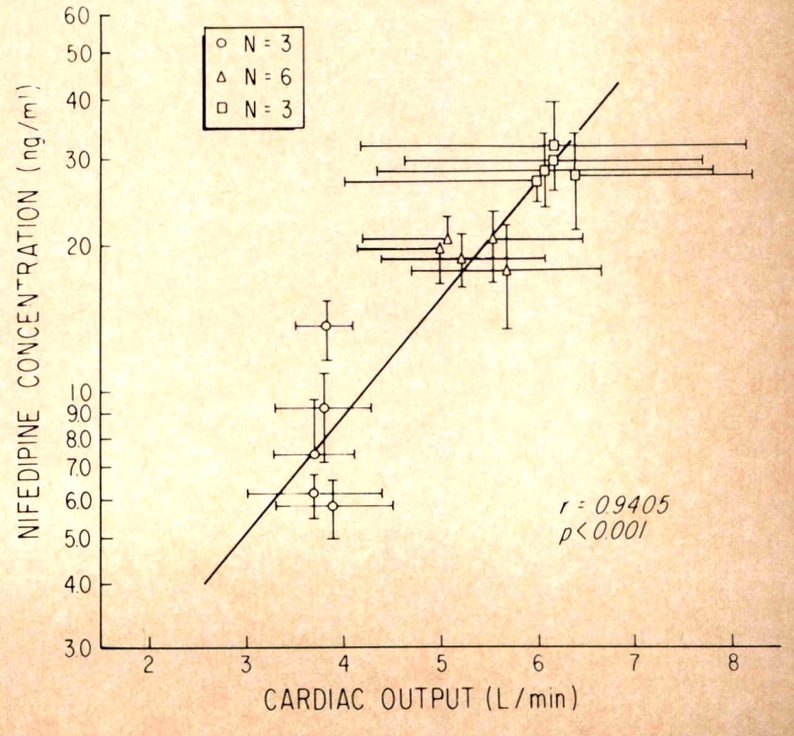

FIGURE 13. Plasma concentrations of nifedipine versus cardiac output. Data were obtained in dogs anesthetized with pentothal. Reproduced with permission from *J Cardiovasc Pharmacol*.[45] No evidence of negative inotropic effects is seen, even at higher drug concentrations, where 50% increase in cardiac output occurs.

ular interest was the observation that bioavailability after initial oral doses (38%) increased to 90% with continued drug administration, without changes in elimination half-time values. Smith et al attributed this observation to saturation of the metabolic elimination pathway for diltiazem.

A similar study involving only single intravenous and oral doses of diltiazem was reported by Hermann et al,[55] who found half-life values of 3.1 hours after both intravenous and oral doses; bioavailability varied from 24 to 74% (mean: 42) due to differences in first-pass effects among subjects.

In patients with advanced renal failure, single doses of diltiazem (120 mg) were eliminated with a half-life of 3.4 hours,[56] not significantly different from findings in normal subjects.

Diltiazem is 80% bound to serum proteins, and binding was independent of drug concentration.[57] Drug binding was not altered by the presence (in therapeutic concentrations) of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid or warfarin.

Preliminary studies in dogs[58] and patients[59] suggest that diltiazem plasma concentrations may be related to both the hemodynamic and electrophysiologic effects of the drug. Further work will be required to define the plasma drug levels associated with specific therapeutic and toxic effects.

Drug Interactions

The calcium-channel blocking drugs are particularly useful in patients with various types of cardiovascular disorders, a population in which polypharmacy is widely practiced and often appropriate. It is not surprising, then, that interactions with other drugs are being observed, some of which may have distinct clinical significance.

When verapamil is added to a regimen that includes digoxin, plasma glycoside concentrations increase about 75%[60,61] because of verapamil-related decreases in digoxin clearance by the kidney.[62] In some clinical studies, this occurrence has been held responsible for an increased incidence of digitalis toxicity,[60,63] although others have not confirmed this.[61] In an animal model, we showed that concomitant administration of verapamil and acetylstrophanthidin markedly *increases* the dose of glycoside required to produce electrophysiologic toxicity, compared with that needed when glycoside is given alone.[64] Therefore, although the pharmacokinetic aspects of the verapamil-digoxin interaction are well demonstrated, the clinical consequences are not at all clear, and the need to decrease glycoside doses when verapamil is added is not well established. A similar interaction between diltiazem and digoxin, in which renal digoxin clearance was reduced and plasma glycoside levels increased, was recently reported.[65] There is more controversy about the results of coadministration of nifedipine and digoxin; whereas Belz et al[66] found an increase in digoxin levels after addition of nifedipine, Pedersen et al[67] reported that nifedipine dosing produced no significant alterations in digoxin pharmcokinetics.

Another area of interest involves interactions between calcium-entry blockers and anesthetics. Although halothane and catecholamines are an established arrhythmogenic combination, Kapur and Flacke[68,69] have shown that verapamil produces a sustained increase in the arrhythmogenic threshold, which persists even when plasma drug concentrations are too low to produce measurable hemodynamic effects. Isoflurane is a volatile anesthetic with myocardial depressant properties that are enhanced by the addition of verapamil.[70] In the isolated rat heart, the combination of halothane and nifedipine appears to produce additive negative inotropic effects,[71] whereas in the intact dog anesthetized with halothane, nifedipine produced marked hypotension due to peripheral vasodilation and attenuated reflex compensatory heart rate increases.[72] During fentanyl-pancuronium anesthesia in patients, the hemodynamic effects of nifedipine included a negative inotropic effect without sustained vasodilation.[73] The pharmacokinetic aspects of these interactions have not yet been studied.

A considerable body of literature is evolving on the combined use of β-adrenoceptor blocking drugs and calcium-entry antagonists. Because nifedipine appears to act predominantly as an arterial vasodilator, its combination with β blockers would appear to be a reasonable attempt to blunt the reflex heart rate increase accompanying drug-related decreases in peripheral vascular resistance; in patients with angina who have reasonable exercise tolerance, this combination was termed by Dargie et al[74] a *beneficial drug interaction.* However, there is evidence that nifedipine does indeed have negative chronotropic and inotropic effects, which are normally masked by compensatory sympathetic activity; in the presence of β blockade, therefore, the potential for electrophysiologic toxicity and depression of left ventricular contractile function may become manifest.[75,76] The combination is, however, widely used and appears to be generally without significant hazard in the absence of profoundly impaired ventricular pump activity.

With verapamil, in contrast, the dose-related negative inotropic effects[77] may be exaggerated when it is given with a β blocker. This was clearly shown in the report from Packer et al,[78] in which patients with angina treated with therapeutic doses of propranolol (producing plasma drug levels >100 ng/ml), were given 40-, 80- and 120-mg oral doses of verapamil; this resulted in dose-dependent decreases in cardiac performance. Repeat administration of the 120-mg verapamil dose after withdrawal of propranolol produced no significant cardiodepressant effects, emphasizing the negative inotropic potential of this drug combination. Furthermore, animal studies in our laboratories have documented a propranolol-related decrease in liver blood flow, which reduces the clearance of verapamil and permits accumulation of the drug to toxic plasma concentrations during continuing verapamil administration.[79] The pharmcokinetic aspects of this interaction are complex and depend upon the order of administration of the drugs, the doses of each used, the plasma

levels produced and the underlying state of the myocardium. Because the potentially toxic effects of the interaction depend to a considerable degree on plasma level-related drug effects, it is not surprising that clinical studies with stable subjects and fixed-dose drug administration protocols have not generally reported deleterious consequences from the combination.[80,81] Similar clinical studies are also appearing for diltiazem–β-blocker combinations, and with similar results.[82] Despite the complex pharmacokinetic results from the coadministration of calcium-entry blockers and β-adrenoceptor antagonists, it seems clear that abolition of sympathetic chronotropic and inotropic influences in the myocardium may permit unwanted actions of the calcium blockers to become manifest[83] and, in addition, that such a combination of drugs must be used clinically with considerable caution.[84]

Cimetidine, which has pronounced effects on both liver blood flow and drug metabolizing enzyme systems, might be expected to alter the elimination kinetics of nifedipine, diltiazem and verapamil, because each calcium-blocker agent is subject to hepatic disposition; no controlled trials have yet been reported.

In summary, the clinical use of verapamil, nifedipine and diltiazem has evolved on a largely empiric basis; the bedside application of these agents has preceded definitions of their clinically relevant pharmacokinetic and pharmacodynamic profiles. However, studies are now appearing that may substantially alter the ways in which these drugs are used. For instance, the demonstration of reduced clearance of verapamil with long-term oral administration implies that twice-daily dosing may be sufficient, in contrast to the 3 or 4 daily doses recommended by the manufacturer. The same may be true for diltiazem, but further studies are required. The importance of intact hepatic function and perfusion status with all these agents has emerged from kinetic studies, resulting in the need for an appropriate degree of clinical caution when the drugs are used in patients in whom liver abnormalities may be present. Furthermore, pharmacodynamic studies relating plasma drug concentrations of each of the 3 available calcium-entry blockers to their observable effects are now being reported. These data, together with pharmacokinetic observations, should assist in efforts to characterize patients who do not respond satisfactorily to therapy into appropriate categories. Interactions with other drugs appear to have both kinetic and dynamic aspects of considerable clinical consequence, especially when β-receptor blockers and the calcium-entry antagonists are given together. Finally, progress in defining the clinical kinetics and dynamics with these prototypic agents should help to focus investigation of newer drugs as they evolve.

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Large Vessel Coronary Vasospasm: Diagnosis, Natural History and Treatment

C. RICHARD CONTI, MD

The diagnosis of coronary artery spasm is confirmed by angiography, for example, change in caliber of the coronary arteries plus evidence of ischemia. The prevalence and contribution of coronary artery spasm in the individual patient with symptoms of ischemic heart disease is not known and depends on how the condition is defined. The prognosis of patients with coronary artery spasm appears to depend on the presence or absence of severe coronary atherosclerosis, that is, those with severe disease have a worse prognosis. Nitrates should be used to initiate therapy in all patients with this problem. Intravenous nitrates have proven useful in patients whose symptoms are difficult to control and who require hospitalization. β blockers used alone may be detrimental in patients with coronary artery spasm, but studies supporting the detrimental effects are few. The combination of nitrates, β blockers and nifedipine has proved effective therapy for many patients with recurrent angina at rest, possibly related to coronary artery spasm. Several open-label and double-blind placebo control trials have shown that all of the calcium antagonists are effective short-term agents for patients with proven coronary artery spasm. When nifedipine was compared with isosorbide dinitrate in a randomized crossover, double-blind trial in patients with coronary artery spasm, both drugs were shown to be efficacious and neither was superior.

The traditional α-blocking agents have not been shown to be an effective therapy, but a recent study of prazosin, a selective α blocker, revealed excellent results in patients whose conditions were resistant to therapy with traditional calcium blockers, β blockers and, in 1 case, phenoxybenzamine. Another study, however, showed no beneficial effect. α-β blockers, anticholinergic drugs, aspirin and prostacylin have not been shown to be effective treatment for coronary artery spasm. In patients with "refractory coronary artery spasm" it may be necessary to use intracoronary nitroglycerin, combinations of calcium antagonist alone or with nitrates, or prazosin therapy to control symptoms. Although the reason is not clear, a few cases have responded to therapy with intraaortic balloon counter pulsation. Coronary artery bypass surgery with and without denervation procedures is effective in many patients with obvious obstructive coronary stenosis, in addition to coronary artery spasm related to the underlying coronary lesions. However, results are not as good in those patients as in patients with fixed coronary stenosis and no evidence of coronary artery spasm.

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It is my belief that coronary artery vasomotion plays an important role in the pathophysiologic features of the various conditions resulting from myocardial ischemia. However, I do not believe that coronary artery spasm is the only mechanism to explain the clinical manifestations of ischemic heart disease. Figure 1 schematically illustrates the theoretical contribution of fixed and dynamic coronary artery stenosis to the origin of myocardial ischemia. Four factors are considered: (1) physiologic features, such as coronary blood flow and myocardial oxygen demand, (2) the percentage of coronary artery stenosis secondary to atherosclerosis, (3) the clinical presentation of angina and (4), postulated mechanism responsible for the ischemic cardiac pain.

At one extreme (Fig. 1, left) is the patient group with normal or near normal coronary arteries. The most common clinical presentation is angina at rest. Because there is no limitation of coronary blood flow caused by atherosclerosis, the most logical physiologic event responsible for this chest pain is a decrease in coronary blood flow rather than an increase in myocardial oxygen demand. Thus, the hypothetical mechanism most likely responsible for chest pain in these patients with "normal" coronary arteries is abnormal constriction of the coronary arteries or vasospasm.

From the Division of Cardiology, College of Medicine, Department of Medicine, University of Florida, Gainesville, Florida.

Address for reprints: C. Richard Conti, MD, Division of Cardiology, College of Medicine, Department of Medicine, University of Florida, Gainesville, Florida 32610.

In contrast, at the other extreme (Fig. 1, right) is the patient group with severe fixed stenosis >90% secondary to coronary artery disease. These patients' chest pain syndrome is most likely related to effort and the physiologic event is increased myocardial oxygen consumption in the setting of fixed coronary reserve. Thus, the mechanism for chest pain in such patients is the presence of severe coronary atherosclerosis.

The patient group in the center of Figure 1 (those with 50 to 60% coronary artery stenosis) may present with chest pain at rest or with variable effort. The physiologic event occurring in these persons is transient decrease in caliber of the coronary arteries producing a decrease in coronary blood flow associated with an increase in myocardial oxygen demand secondary to exercise. Thus, the most likely mechanism is related to the combination of significant artery disease plus vasomotion abnormalities of the coronary arteries.

The patient group that presents with prolonged angina at rest is represented in Figure 1, far right. These are the type of persons who could be considered as having an unstable condition or being in the process of evolving myocardial infarction. As many studies indicate, patients with unstable angina and evolving myocardial infarction generally have significant atherosclerosis. It is possible that a slight change in caliber of the arteries, such as increased tone, may transiently occlude coronary blood flow without any corresponding increase in myocardial oxygen demand and thus produce severe ischemia. It is also possible that a transient thrombosis of this severely narrowed coronary artery may produce the same result, for example prolonged angina at rest. If the tone is relaxed or the thrombosis is lysed, then this severe chest pain syndrome can be called unstable angina. If the increased tone persists or the thrombosis is not lysed, then an acute evolving myocardial infarction will result.

Any unstable ischemic syndrome can develop from any of these clinical presentations. For example, the patient with normal or near normal coronary arteries can have repetitive episodes of coronary artery spasm that make his condition unstable, thus putting him into the same category as the patient with severe coronary stenosis and mild changes in tone or repetitive episodes of thrombosis. In this fourth category with severe stenosis and either increased tone or repetitive thrombosis, the major mechanism is related to the presence of severe coronary artery disease.

Diagnosis of Coronary Artery Spasm

Some confusion exists because the term *coronary artery spasm* has been used interchangeably with the specific clinical syndrome of *variant angina* or *Prinzmetal's angina pectoris*. The term variant angina should be reserved for patients whose only symptoms are chest pain at rest associated with transient ST-segment elevation on the electrocardiogram (ECG). This is a relatively uncommon clinical presentation of angina pectoris.

I have found the following to be a useful working definition of coronary artery spasm: a transient decrease in lumen diameter of an epicardial coronary artery of sufficient degree to produce myocardial ischemia, in the absence of increased heart rate and blood pressure, which is promptly reversed by nitroglycerin. This definition does not set limits on the degree of lumen diameter decrease required to produce ischemia, and it can be applied to patients with normal as well as diseased coronary arteries. The frequently associated manifestations of myocardial ischemia are chest pain and ST-segment elevation or depression on the ECG. However, neither symptoms nor ST-segment elevation are always present during repeated episodes of angina in the same patient who, on other occasions, may have ST-segment elevation and associated coronary lumen decrease.

Coronary artery spasm should not be diagnosed unless there is evidence, such as angiography and ischemia,

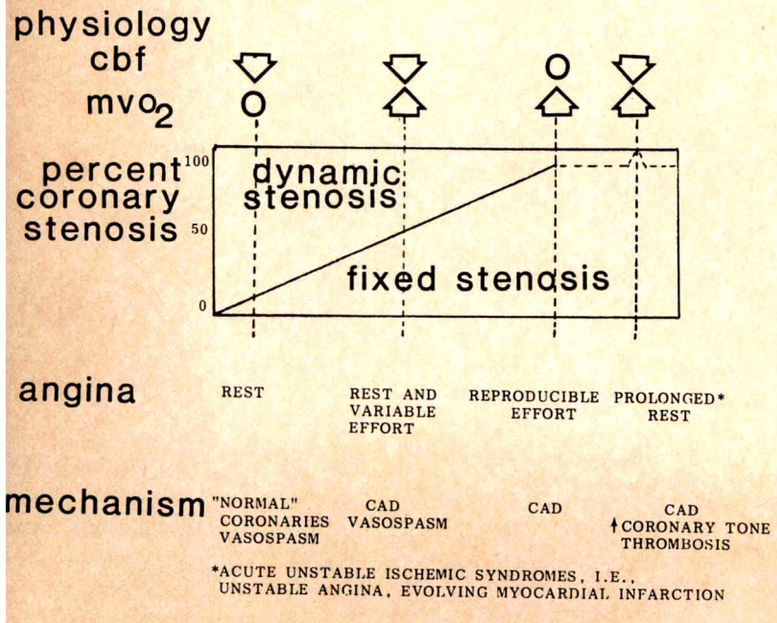

FIGURE 1. Schematic illustration of theoretical contribution of fixed and dynamic coronary artery stenosis to etiology of myocardial ischemia. CAD = coronary artery disease; CBF = coronary blood flow; $M\dot{V}O_2$ = myocardial oxygen demand.

TABLE I "Natural" History of Coronary Artery Spasm

Study	Diagnosis	Patients (n)	Mean Duration of Follow-Up	Death	Myocardial Infarction	Angina	Remission
Selzer et al[1]	Variant angina	16	...	3	1	...	...
Severi et al[2]	Angina at rest	138	4 years	12	32	...	...
University of Florida	Coronary spasm	27	1 year	3	5	4	15
Waters et al[3]	Variant angina	132	1 month	5	13	...	...
Bott-Silverman et al[4]	Coronary spasm	59	6 years	0	11	25	23
Waters et al[5]	Variant angina	169	12 months	19	34	...	...
Waters et al[6]	Variant angina	100	12 months	...	...	55	45

to support the diagnosis. This evidence can be obtained at the time of coronary angiography if the patient has spontaneous angina pectoris or if angina is provoked by an agent such as ergonovine maleate. Patients with chest pain and transient ST-segment elevation on routine exercise or ambulatory ECG should be presumptively diagnosed as having coronary artery spasm.

Unfortunately, ST-segment elevation does not prove that patients have coronary artery spasm. However, it does suggest that angina is related to transient decrease in myocardial blood flow. The mechanism of the transient decrease in blood flow may differ according to coronary anatomy. For example, in a patient with normal coronary arteries or <50% stenosis, the most likely cause of ST-segment elevation is spasm. Thrombotic occlusion theoretically could occur in the setting of prolonged spasm and a myocardial infarction could evolve. In a patient with >50% but <70% stenosis of the coronary artery, spasm and subsequent thrombosis may still occur. However, because of the significant coronary artery disease, stasis and turbulence may enhance platelet aggregation and thrombosis could occur in the absence of spasm. In a patient with >70% and <90% stenosis, turbulent flow, stasis and platelet aggregation can account for in situ thrombosis as a primary mechanism, but the possibility of spasm as well should not be excluded. In the patient with >90% stenosis of the coronary artery, it is reasonable to hypothesize that coronary artery thrombosis occurs as a primary event. This concept is illustrated in Figure 2. If the thrombosis is transient, the patient might have transient ST-segment elevation and be labeled as having either Prinzmetal's or unstable angina. If the thrombosis is permanent, myocardial infarction may evolve.

A probable diagnosis of spasm can be considered in patients who have the syndrome of variant angina, that is, angina at rest, associated with ST-segment elevation on the ECG. A high degree of suspicion for coronary artery spasm exists in patients who have angina at rest, especially those with unstable angina. Additionally, one can be suspicious of spasm in patients who have variable effort angina or walk-through angina. Coronary artery spasm is a possibility in patients with acute myocardial infarction or acute reinfarction and in patients with normal coronary arteries who die suddenly.

Natural History

It is unlikely that patients with coronary spasm are a homogenous group. A common variable is the presence or absence of severe coronary artery disease. Although only a few reports are available, it seems as though spasm in association with coronary artery disease has a more malignant course than does coronary spasm in patients with minimal or no coronary disease. However, a few cases of coronary vasospasm in patients with normal coronary arteries have resulted in ventricular fibrillation and heart block, so that even in this setting, the condition is not benign. Results of several reports are listed in Table I.

Selzer et al[1] reported observations in 16 patients with variant angina. Nine patients with minimal or no coronary artery disease had no serious events during follow up. In contrast, 4 of 7 patients with coronary artery disease had an acute myocardial infarction, and 3 of these patients died. Severi et al[2] studied 138 patients, 9 of whom had angiographically normal coronary arteries. In the first month of follow up, 28 had nonfatal myocardial infarctions and 5 died. From 1 to 4 years after therapy, 7 additional patients died and 4 had acute myocardial infarction. At the University of Florida, 27 patients with coronary artery spasm and coronary artery disease were treated with calcium antagonists for 1 year. During the course of follow up, 3 died, there were 5

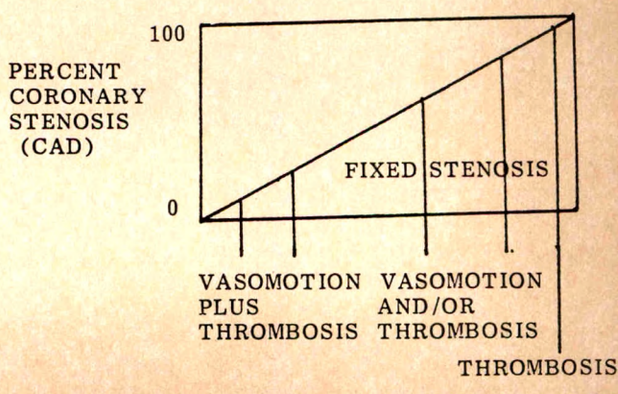

FIGURE 2. Theoretical relation of coronary artery disease, vasomotion and thrombosis in patients with myocardial infarction. CAD = coronary artery disease.

nonfatal myocardial infarctions, 4 patients had severe angina pectoris requiring hospitalization and 15 had a "good response" to medical therapy.

Waters et al,[3] at the Montreal Heart Institute, reported the prognosis of 132 patients with variant angina at 1-month follow up. Most of the patients were treated with calcium antagonists. Five patients died and 13 had nonfatal myocardial infarction. Of the remaining 114 patients, none either had a myocardial infarction or died. The investigators noted a tendency toward single-vessel disease in patients without myocardial infarction or death and multiple-vessel disease in the 18 patients who died or had myocardial infarction. Bott-Silverman and Heupler[4] reported the clinical course of 59 patients with coronary spasm with angiographically normal or near normal coronary arteries. Average follow-up time was 5.9 years. They noted spontaneous remission in 39% of patients; 24% were long-term and 15% were short-term. In addition, 19% of patients had a myocardial infarction, 10% required permanent pacemakers and no patient died.

Waters et al[5] reported a study of 169 consecutive patients hospitalized for variant angina who were studied for a mean of 15.3 months (range 1 to 68). At 1 year, the survival rate was 95% but there was a 20% nonfatal myocardial infarction rate. At 3 years, the overall survival rate was 87%. Most complications occurred within the first 3 months after diagnosis.

Waters et al[6] also assessed the prevalence of spontaneous remission in 100 patients with variant angina with a follow up of at least 1 year. Remission was diagnosed in 45 of the 100 patients who had been angina-free and who had no treatment for >3 months (mean 18.3). Based on these observations, the investigators believe that variant angina should be considered a "temporary condition." They advise that "drug therapy can probably be discontinued at some point in most patients with a history of variant angina," and they usually begin to taper and discontinue treatment 6 to 12 months after angina disappears.

Treatment

Current Drug Therapy for Patients With Proved or Suspected Coronary Artery Spasm

The goal of therapy for patients with proven coronary artery spasm should be the prevention of myocardial ischemia rather than prevention of recurrent attacks of pain, because myocardial ischemia can occur in the absence of chest discomfort. Ideally, it is desirable to have an objective endpoint of therapy, for example, decrease in frequency of ST-segment shifts with or without pain. Theoretically, prevention of myocardial ischemia episodes should result in a decrease of malignant ventricular arrhythmias and, possibly, a decrease in the incidence of myocardial infarction and sudden death.

Nitrates: Perhaps the best way to initiate therapy, regardless of clinical presentation or ECG manifestations, is with nitrates. Traditionally, long-acting, sublingual, oral or topical nitrates have been used to prevent recurrent episodes of angina at rest, whereas individual attacks have been treated with sublingual nitrates.

The recent availability of commercially prepared intravenous glyceryl trinitrate has facilitated the management of many acute cardiac conditions, including recurrent angina at rest. Page et al[7] treated 67 patients with an intravenous preparation. Therapy was initiated during the first days of hospitalization and the dose was increased every 10 to 30 minutes from 36 to 108 μg/min. Systolic arterial pressure was maintained >90 mm Hg. Intravenous nitrates were used in combination with β blockage in 34 patients and with nifedipine in 6 additional patients. In 21 patients, ECG changes were those of variant angina, that is, transient ST-segment elevation. The investigators noted a decrease in the mean number of anginal attacks from 9.83 ± 7.6 (previous 7 days) to 1.2 ± 2.45. The duration of treatment with intravenous nitrates varied from 2 to 29 days (mean: 7.4 ± 4.2). Sixty-four patients (95.5%) had improvement in symptoms during treatment with intravenous nitrates, 42 (62.7%) becoming free of pain, but 3 continued to have angina at the same rate as before nitrate therapy. Complications were noted in only a few patients; bradycardia and hypotension occurred in 2. These symptoms were reversed by decrease of infusion rate. Headaches were noted in 3 patients, requiring a decrease in the nitrate dose.

Beta blockers: In the experience of most clinicians, β blockers seem to control the symptoms of recurrent angina at rest regardless of the direction of the ST-segment shift during chest pain. It is not entirely clear why this should be the case. However, it must be remembered that β blockers have some effects that favorably influence perfusion of ischemic myocardium and prevent arrhythmias. For example, propranolol decreases platelet aggregation across the myocardium at rest and during pacing-induced tachycardia. It is also possible that factors initiating coronary vasospasm may be blocked by β-blocking agents. An additional factor that may account for the success of β blockers in treating this condition is the concomitant use of nitrates. Most physicians treating patients with recurrent angina use oral, topical or intravenous nitrates simultaneously with β blockers. Although the studies are few, one must acknowledge the potential detrimental effect on β blockers in patients with proven coronary artery spasm. Robertson et al,[8] using a double-blind protocol, investigated the use of propranolol in patients with coronary artery spasm as assessed by subjective and objective variables. Both small-dose (40 mg every 6 hours) and large dose (160 mg every 6 hours) propranolol were administered. At both doses, the duration of angina attacks was significantly prolonged but the frequency was not. There was considerable variability of patient response.

The β blockers that are relatively specific in low doses for the β_1 receptor warrant a trial in patients with coronary artery spasm. Some new β-blocking drugs possess intrinsic sympathomimetric activity. These agents act as β-receptor agonists as well as antagonists, so that the heart rate at rest tends to remain unchanged or even increase. These agents may provide the vasodilating

stimulus necessary to prevent coronary spasm. Current wisdom dictates that β blockers should not be used without a vasodilator in patients with proven coronary artery spasm.

Calcium antagonists: Most investigators report that patients with chest pain that is due to coronary artery spasm, who have continued symptoms despite nitrate and β blocker therapy, respond favorably to calcium-antagonist therapy.

Results using nitrates, β blockers and nifedipine: Hugenholtz et al[9] recently reported on 73 patients with unstable angina treated with maximum β-adrenergic blockade, nitrates and bed rest. Fifty-two of these patients remained symptomatic. After 60 mg of nifedipine administered orally for 24 hours was added to treatment, 42 patients became asymptomatic. The excellent clinical response to the drug in this group of patients with unstable angina pectoris indicates that calcium antagonists may play an important role in therapy, particularly when the cause of angina is suspected to be related to abnormal coronary vasomotion. Gerstenblith et al[10] randomly allocated 138 patients with unstable angina to either routine therapy with nitrates and β blockers or routine therapy with nitrates, β blockers and nifedipine. They showed that fewer patients had medical therapy failures (myocardial infarction, death or surgery) when given nifedipine compared with routine therapy. This difference was due primarily to the 52 patients who had transient ST-segment elevation associated with chest pain.

Antman et al[11] evaluated nifedipine in a large, open-label trial in patients with coronary artery spasm. They reported results of therapy in 127 patients with either angiographically documented coronary artery spasm, angina at rest with reversible ST-segment elevation or both. The patients were treated with nifedipine in dosage ranges from 40 to 160 mg/day. Other therapy, such as nitrates or β blockers or both, were continued or added to the treatment in many instances. Follow-up time averaged 9 months and 87% of patients had at ≥50% reduction in angina frequency; in 63%, angina was abolished.

Results using verapamil as monotherapy: Mehta et al[12] reported similarly encouraging results using the calcium-antagonist verapamil over a 5-day period. No therapy other than sublingual nitrates was used in the patients, and nitrates were used to treat individual attacks of pain. In this study, verapamil was compared with placebo in 15 patients, 4 who had ST-segment elevation with pain and 11 who had ST-segment depression with pain. Thirteen of these patients had >50% decrease in angina frequency when verapamil was compared with placebo. One patient had >50% decrease in angina frequency when placebo was compared with day 1 of the trial and 1 patient had no change in angina frequency when verapamil was compared with placebo, regardless of the dose of verapamil used. These results indicate that verapamil was an effective short-term agent for the management of patients admitted to the hospital for treatment of angina at rest.

Results using diltiazem: Because of a favorable preliminary report by Yasue et al,[13] a double-blind intervention using 2 dose schedules of diltiazem, 120 and 240 mg/day, in 11 patients with variant angina was performed.[14] With small dose therapy, 5 patients became asymptomatic or had >50% decrease in symptoms compared with placebo. When large-dose therapy was used, 6 patients became asymptomatic and 1 had >50% decrease in angina frequency. Diltiazem appeared to be remarkably free of adverse effects during this short-term trial. No patient showed evidence of rebound or increase in symptoms after withdrawal of this drug.

Results of comparison between nifedipine and isosorbide dinitrate in patients with coronary spasm[15]*:* The subjects for this study were 22 men and 4 women who had angina that occurred mostly at rest and was relieved by nitroglycerin. There was a 2-week lead-in phase during which calcium antagonists or topical nitrates or both were excluded from the treatment regimen. Patients who had >3 episodes of pain/week were entered into the double-blind randomized phase (treatment with either niefdipine or isosorbide dinitrate). After dose titration (40 to 120 mg/day) and evaluation, they were given the alternate therapy. During the course of the trial, the effects of nifedipine and isosorbide dinitrate on frequency of angina and consumption of nitroglycerin were evaluated by patient diary. Twenty-one patients completed all study phases. Two patients died, 1 in each group. Two patients could not tolerate isosorbide dinitrate because of headache and hypotension and an additional patient stopped the study medication because of poor response. In the 21 patients who completed all 3 study phases, the mean frequency of angina during the lead-in phase was 1.86 episodes/day. Compared with lead-in phase, the frequency of angina was significantly decreased for both nifedipine (0.71 episodes/day) and isosorbide dinitrate (0.66 episodes/day) (in both, $p < 0.05$). Likewise, nitroglycerin consumption was significantly decreased in the lead-in phase (2.09 tablets/day) when compared with both nifedipine (0.90 tablets/day) and isosorbide dinitrate (0.56 tablets/day) phases (in both, $p < 0.05$).

Individual patient responses to the drugs were analyzed. Compared with lead-in phase, angina frequency during the nifedipine phase was reduced by ≥50% in 18 of 24 patients. Six of these were asymptomatic. During the isosorbide dinitrate phase, 15 of the 21 patients had a >50% decrease in their angina frequency and 4 of these were asymptomatic. Eleven patients had this decrease in angina frequency during both nifedipine and isosorbide dinitrate phases. In addition, 6 patients receiving nifedipine and 6 patients taking isosorbide had <50% decrease in angina frequency.

When the entire group of 21 patients who completed all study phases was evaluated, 11 had >50% decrease in angina frequency with nifedipine compared with isosorbide dinitrate and 7 had >50% decrease in angina frequency with isosorbide dinitrate compared with nifedipine. The remaining 3 patients had a similar angina frequency with both drugs. This trial indicated that both nifedipine and isosorbide dinitrate were effective in certain patients with coronary spasm and neither drug was clearly superior.

Result of calcium-antagonist therapy in Japan: Although the aforementioned studies illustrate the effectiveness of these agents in the United States alone, practitioners around the world attest to their clinical usefulness. Kimura and Kishida[16] reviewed data from 11 cardiology institutes in Japan to determine the effectiveness of drug therapy, especially with calcium antagonists, in variant angina patients. The subjects were 243 men and 43 women. Coronary artery disease was found in 92 of 162 patients (56.7%) in whom coronary angiography was performed. Drugs were effective in 92.3% of patients with normal or near normal coronary arteries and 82.6% of those with >50% stenosis. The investigators interpret these findings to suggest that the drugs are effective because of their antispsamotic action.

Alpha-blocking agents: Alpha-blocking agents have received isolated and anecdotal attention, suggesting that they may be effective in preventing coronary spasm. If the α-adrenergic nervous system plays a major role in the genesis of coronary spasm in an individual patient, this mode of therapy would seem to be the logical choice. However, some experiences suggest that few patients respond to α-blockade therapy.

Recently Tzivoni et al[17] reported the successful treatment of Prinzmetal's angina in 6 patients using the selective α blocker prazosin. Therapeutic trials with large doses of nifedipine, verapamil, nitrates, β blockers and, in one case, phenoxybenzamine were ineffective in all 6 patients. Prazosin, 8 to 30 mg/day, combined with small-dose nitrates or nifedipine completely abolished the attacks in 4 patients, markedly reduced their frequency and intensity in 1 patient and had to be stopped in the sixth because of hypotension and dizziness. In 4 patients, discontinuation or decrease of prazosin resulted in exacerbation of symptoms but its renewal was followed by disappearance of the attacks. Mean follow-up period in the study was 4 to 6 months. Despite these encouraging results, Winniford et al[18] reported no obvious beneficial effect in 6 patients with variant angina randomized to prazosin or placebo over a 4.5-month period. Mean dose of prazosin was 14.0 ± 2.4 mg/day.

Alpha-beta-blocker therapy: A new class of adrenergic-blocking agents possesses both α- and β-blocking activity. Labetolol is the prototype agent of this class. In a recently published preliminary trial,[19] labetolol was reportedly effective in significantly reducing or abolishing the frequency of "spontaneous angina." If these episodes were due to coronary artery spasm, labetolol may warrant further study.

Anticholinergic therapy: Based upon reports largely from Japan, the cholinergic nervous system is implicated as the basis for coronary artery spasm in certain patients. Therefore, trials with anticholinergic agents were suggested. To date, the reports have been isolated and anecdotal, and some trials have shown that these agents are not useful in most patients with coronary artery spasm.

Results of antiplatelet therapy for coronary spasm: The observation that coronary spasm occurs frequently at sites of minimal atherosclerosis has led to the suggestion that vascular endothelium produces deficient amounts of PGI_2 in these atherosclerotic areas. Under conditions in which platelet adhesion and aggregation are increased, release of thromboxane A_2 would result in vasoconstriction. Increased peripheral levels of thromboxane B_2, the stable metabolite of thromboxane A_2, have been reported in some patients with variant angina. Because of these findings, treatment with antiplatelet agents has been suggested.

Chierchia et al[20] hypothesized that thromboxane A_2 released by aggregating platelets was a potential mediator of coronary vasospasm. They studied 7 patients with coronary artery spasm by continuous ECG monitoring for 2 days before and 2 days after a single small intravenous dose of aspirin (2 mg/kg). This dose reduced thromboxane B_2 to <3% of the control values. There were 129 transient ischemic episodes during control and 146 during aspirin therapy, when platelet thromboxane B_2 was reduced to negligible levels. Because the duration, severity and incidence of symptomatic episodes were not significantly affected by small-dose aspirin, thromboxane A_2 is probably not responsible for initiation of coronary vasospasm. In another study by Miwa et al[21] aspirin, 4 g/day, was administered orally to 4 patients with Prinzmetal's angina. The administration of aspirin markedly increased the frequency of angina attacks and attacks that had occurred only at night or in early morning during the control period also occurred in the daytime when the 4 patients were receiving aspirin. Exercise stress testing performed in the afternoon was repeatedly negative during the control period; it became positive during aspirin administration in 3 patients who were able to perform the test. The investigators concluded that a large amount of aspirin can aggravate coronary arterial spasm in cases of Prinzmetal's angina. Despite these negative observations, the concept that platelet aggregation may be responsible for initiating or aggravating spasm should not be ignored.

Several other methods to inhibit platelet aggregation are available, for example, other nonsteroidal antiinflammatory agents, stable PGI_2 analogues, PGI_2-releasing agents and specific inhibitors of thromboxane A_2. It should also be mentioned that certain calcium-blocking agents, in particular, verapamil and diltiazem, inhibit platelet aggregation. Studies of platelet-aggregation inhibitors should shed new light on the mechanisms of coronary spasm and provide avenues for treatment. At present, however, these agents are not recommended for the usual management of the patient with coronary artery spasm.

Effect of intravenous prostacyclin: Chierchia et al[22] evaluated the effects of intravenous PGI_2 in 9 patients with variant angina and 6 normal volunteers. In the normal subjects, with PGI_2 in 2.5, 5, 10 and 20 μg/kg/min, there was a significant antiplatelet effect and a dose-dependent decrease in both systolic and diastolic arterial pressure with a corresponding increase in heart rate. In 8 patients with proven coronary artery spasm, PGI_2 did not affect the number, severity or duration of spontaneous ischemic episodes due to coronary vasospasm. However, in 1 patient, the number of ischemic

TABLE II Medical and Surgical Treatment of Patients With Coronary Stenosis and Evidence of Coronary Artery Spasm

Report	Patients (n)	Early or Perioperative Death	Early or Perioperative Myocardial Infarction	Average Follow Up	Late Death	Late Myocardial Infarction	Angina	Decreased or No Angina
University of Florida								
Surgical	21	1	1	3.5 years	1	2	9	10
Medical	27	2	0	3.5 years	2	2	17	6
"Surgical" Reports[28]	89	12	13	12.2 months	2	0	24	51
Pasternak et al[29]								
Surgical	38	3	3	32.3 months	2	2	5	28
Medical	16	0	1	32.3 months	1	0	7	8
Schick et al[30]								
Surgery								
Preinfarction	40	0	7	30 months	0	0	10	30
Recent infarction	12	3	...	30 months	0	2	2	7
NHLBI trial[27]								
Surgical	37	6	...	42 months	0	10	5	26
Medical	42	3	...	42 months	0	6	29	10
Bertrand et al[31]								
CABG	13	2	1	36 months	...	...	2	10
CABG plus plexectomy	22	2	0	20 months	...	...	1	19

CABG = coronary artery bypass graft; NHLBI = National Heart, Lung, and Blood Institute.

episodes was consistently reduced during 4 consecutive periods of PGI_2 infusion alternated with placebo. The investigators conclude that while PGI_2 can be administered safely and may occasionally result in complete disappearance of ischemic episodes due to coronary vasospasm, it is usually ineffective.

Treatment of "refractory" coronary artery spasm: In Prinzmetal's description of variant angina,[23] he suggested that responsiveness to nitroglycerin was part of this syndrome. This idea is widely held. However, we recently studied 4 patients with coronary artery spasm who did not respond to the usual dosages of sublingual or intravenously administered nitroglycerin. In 2 of these patients, coronary artery spasm occurred in the right coronary artery, and in the other 2, spasm occurred in the anterior descending branch of the left coronary artery. Three of these patients (2 with right coronary spasm and 1 with anterior descending spasm) had hemodynamically important atherosclerotic obstruction at or near the site of spasm. In 3 of these patients, the refractory spasm occurred spontaneously during or shortly after coronary angiography, and in 1 the coronary spasm was provoked using ergonovine. In each case, coronary spasm responded promptly to *intracoronary* administration of small doses of nitroglycerin (25 to 100 μg). In 1 case, coronary spasm continued to recur at 25- to 30-minute intervals and was finally prevented with the institution of intraaortic balloon pumping. Whenever the balloon pump was transiently turned off, spasm recurred. The reason for the effectiveness of balloon pumping in this instance is unclear, but perhaps is related to the increased diastolic perfusion pressure in the affected coronary artery.

Recently, Buxton et al[24] reported on 5 patients with refractory ergonovine-induced coronary spasm. Three of these patients died, but in 2, intracoronary administration of nitroglycerin promptly reversed spasm. Maseri et al,[25] in a description of patients with unstable angina, reported on 6 patients in whom acute myocardial infarction developed shortly before, during or after coronary angiography. In these patients, intracoronary nitroglycerin was not effective in reversing spasm. Oliva and Breckinridge[26] identified 6 patients in whom intracoronary nitroglycerin reversed coronary spasm during the early phase of acute infarction. These reports stimulate speculation that refractory coronary artery spasm may be an important step in the evolution of myocardial infarction, sudden death and other ischemic heart disease syndromes.

Comparison of Medical and Surgical Treatment of Patients with Coronary Artery Stenosis and Evidence of Coronary Artery Spasm

With the exception of the National Heart, Lung, and Blood Institute trial for unstable angina,[27] published reports on the medical and surgical management of coronary artery spasm do not compare therapies. Rather, they chronicle events occurring in patients receiving medical or surgical treatment. Table II summarizes these reports.

Over the past 4 years, 21 patients at the University of Florida with coronary artery disease and coronary artery spasm underwent coronary artery bypass graft. Twenty patients survived the operation and 1 had a perioperative myocardial infarction. Of the 20 survivors, followed for an average of 3.5 years, 2 had a subsequent myocardial infarction, 1 died, 10 continued to have angina and 9 were symptom-free.

Surgical reports, from 1971 to 1977,[28] indicate that 89 patients underwent coronary artery bypass graft surgery for angina associated with ST-segment elevation. During a mean follow-up time of 12.2 months, there were 14 deaths and 13 nonfatal myocardial infarctions. Of the survivors, 24 continued to have angina and 51 were symptom-free.

Pasternak et al[29] studied 54 patients with variant angina, 38 of whom underwent coronary artery bypass surgery. Total follow-up time in these patients averaged 32.3 months (range: 7 to 79). Of the 38 patients undergoing surgery, there were 3 hospital deaths (7.8%), 3 hospital myocardial infarctions (7.8%), 2 late deaths and 2 late myocardial infarctions. Over the long-term follow

up, they reported improvement in symptoms in 28 of 33 survivors of surgery (85%). In the 16 patients who did not undergo surgery, there was 1 hospital myocardial infarction and 1 late death. In the 15 survivors, 8 (53%) had satisfactory control of their symptoms. Based on these observations, the authors recommend coronary artery bypass graft surgery in those patients with variant angina who have severely stenotic, fixed atherosclerotic lesions and in whom medical management has failed.

Schick et al[30] published in 1982 the results of surgery in 52 patients with coronary artery spasm and coronary artery disease. All surgery took place from 1973 to 1979. They divided their patients into those who had angina without infarction (40) and those who had angina in the early postinfarction state (12). Of the 40 patients with angina without infarction, there was a mean follow-up time of approximately 30 months. There were no deaths, 7 nonfatal myocardial infarctions and 33 patients without a significant event in this group. In the same group, 10 continued to have angina syndrome and 30 were symptom-free. In contrast, in the 12 postinfarction angina patients, mean follow-up time was also approximately 30 months but 3 patients died and 2 had another nonfatal myocardial infarction. Seven patients were alive without subsequent event. Of the 9 patients alive, 2 continued to have angina and 7 were symptom-free.

In the National Heart, Lung, and Blood Institute trial,[27] 79 patients had chest pain associated with ST-segment elevation. Mean follow-up time was 42 months for both the 42 patients treated medically and the 37 patients treated surgically. In the medical group there were 3 deaths, 6 nonfatal myocardial infarctions and 33 patients who had no events. Of the 39 surviving patients, 29 continued to have angina syndrome and 10 were symptom-free. In contrast, in the 37 surgically treated patients there were 6 deaths, 10 nonfatal myocardial infarctions and 21 patients without a significant event. Of the 31 survivors, 5 continued to have angina and 26 were symptom-free.

In 1980, Bertrand et al[31] published their study comparing coronary bypass surgery with coronary artery bypass graft plus plexectomy in patients with coronary artery spasm and coronary artery disease. The mean follow-up time of the 13 patients undergoing coronary artery bypass graft was 36 months. In this group there was 1 nonfatal myocardial infarction, 2 deaths, 2 who continued to have angina and 2 who were documented as having continued coronary artery spasm. In the 22 patients undergoing coronary artery bypass graft and plexectomy, the mean follow-up time was 20 months. There were no nonfatal myocardial infarctions; there were 2 deaths, 1 continued to have angina and 1 was documented as having coronary artery spasm.

Based on these reports, it seems reasonable to try vigorous dilator therapy before surgery in these patients. If pain or asymptomatic myocardial ischemia persists despite drug therapy, the patient should be considered for coronary artery surgery. However, current results of surgery for patients with this condition may not be as good as those in patients who have typical effort angina and no evidence of coronary artery spasm. Although speculative, this difference may be due in part to spasm occurring along the entire length of the coronary artery, proximal and distal to a fixed obstruction. If surgery is performed, coronary vasodilator therapy should be continued postoperatively with the goal of decreasing the possibility of recurrent coronary artery spasm distal to the bypass graft insertion or in other vessels.

In summary, most patients with syndromes related to coronary spasm respond to nitrates. Nitrates are extremely safe, thus their use for relief or prevention of the acute ischemic episode remains the initial treatment of choice. When symptoms are more than mild-to-moderate in severity or unacceptably controlled in frequency using nitrates alone, other pharmacologic measures are needed. In patients who also have effort angina, suggesting a hemodynamically important atherosclerotic type obstruction in addition to spasm, β-adrenergic–blocking drugs can be helpful. If effort angina remains unacceptably controlled or adverse effects occur, calcium antagonists may be added or substituted. Where the predominant symptom is angina at rest and the patient has other evidence suggesting coronary artery spasm, use of a calcium antagonist usually produces a favorable response. This therapy should be extended not only to patients in whom spasm occurs spontaneously, but also to those in whom it can be provoked by such stimuli as effort or cold. When spasm is superimposed upon hemodynamically important atherosclerotic obstruction, the favorable response to calcium antagonists may not be as great as that seen when spasm exists alone. In these cases, coronary artery bypass surgery may be required to control symptoms. Recommendation for surgery, however, requires demonstration that spasm is occurring in and about the area of fixed atherosclerotic obstruction and not occurring in other vessels or over the entire course of distal vessel.

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Chest Pain and "Normal" Coronary Arteries—Role of Small Coronary Arteries

RICHARD O. CANNON III, MD, MARTIN B. LEON, MD, RITA M. WATSON, MD, DOUGLAS R. ROSING, MD, and STEPHEN E. EPSTEIN, MD

To study the mechanism of chest pain in patients with insignificant epicardial coronary artery disease, 50 patients underwent great cardiac vein (GCV) flow, oxygen content and lactate determinations at rest and during pacing, and left ventricular end-diastolic pressure (LVEDP) measurements at rest and after pacing. Twenty-four patients having typical chest discomfort during pacing demonstrated significantly lower increase in flow from baseline (36 ± 18% versus 86 ± 24%, p <0.001) and decrease in coronary resistance (−17 ± 12% versus −43 ± 7%, p <0.001) compared with 26 patients without pacing-induced chest pain, despite no significant difference in myocardial oxygen consumption ($M\dot{V}O_2$) between the 2 groups. Lactate consumption at a heart rate (HR) of 150 beats/min was significantly less (28.3 ± 21.5 versus 51.3 ± 35.8 mM·ml/min, p <0.001) and the increase in LVEDP from rest to after pacing was significantly greater (5 ± 2 versus 1 ± 2 mm Hg, p <0.001) in the chest pain group. After administration of ergonovine, 0.15 mg intravenously, to 46 of these patients, 31 had typical pain either at rest (1 patient) or during pacing. This group had significantly lower increase in flow (38 ± 20% versus 107 ± 38%, p <0.001), and decrease in coronary resistance (−16 ± 12% versus −45 ± 11%, p <0.001) compared with the 15 patients not having chest pain, despite no significant difference in $M\dot{V}O_2$ between the 2 groups. Patients with chest pain also had lower lactate consumption at a HR of 150 beats/min (39.2 ± 23.6 versus 65.3 ± 46.3 mM·ml/min, p <0.01), greater arterial-GCV oxygen difference (12.5 ± 1.3 versus 11.6 ± 1.0 ml O_2/100 ml, p <0.05), and a more marked increase in LVEDP from rest to after pacing (11 ± 3 versus 5 ± 2 mm Hg, p <0.001). Quantitative coronary arteriography demonstrated no significant luminal narrowing of the epicardial coronary arteries in response to ergonovine. These data are consistent with the hypothesis that some patients with chest pain and angiographically normal epicardial coronary arteries have dynamic abnormalities of the small coronary arteries or coronary microcirculation that cause abnormal vasodilator reserve or vasoconstriction, resulting in myocardial ischemia and angina pectoris. (Am J Cardiol 1985;55:50B–60B)

Angina pectoris in patients whose epicardial coronary arteries appear to be normal or near normal with angiography is a frequent clinical occurrence. In fact, one fourth of the patients entered prospectively into the Coronary Artery Surgical Study (CASS) fell into this category.[1] Although some of these patients may have epicardial coronary artery spasm,[2] this subset is probably quite small because Prinzmetal's or variant angina is relatively uncommon.[3] Despite multiple explanations for chest pain in the presence of normal coronary arteries, an extensive evaluation often fails to reveal an alternative cardiac or noncardiac mechanism, a frustrating experience for both physician and patient.

From the Cardiology Branch, Cardiovascular Diagnosis Section, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Richard O. Cannon III, MD, Room 7B-15, Building 10, National Institutes of Health, Bethesda, Maryland 20205.

Since 1982 we have evaluated over 50 patients with chest pain and angiographically normal coronary arteries. The pain described was usually qualitatively similar to ischemic cardiac pain: it was located substernally, often radiated to the neck and arms and frequently was associated with shortness of breath. The pain was "atypical" only in that its threshold of onset was variable, it often occurred at rest and occasionally nocturnally and was variably relieved by nitrates. Patients often said chest pain occurred toward the end of the day or after strenuous activity. The results of our studies designed to elucidate a possible cardiac mechanism for these patients' chest pain are presented.

Methods

Fifty consecutive patients with chest pain syndromes but with normal epicardial coronary arteries and no known heart disease were evaluated using the protocol described later. The

TABLE I Clinical Profile of Patients Entering Study

Characteristic	NVR (n = 13)	AVR (n = 37)
Hypertension	3	10
Cigarette use		
Active	0	9
Remote	4	5
Diabetes mellitus (insulin-requiring)	0	4
Myocardial infarction	0	6
Alcohol abuse	0	6
Raynaud's phenomenon	0	2
Migraine headaches	0	1
Mitral valve prolapse	1	2
History of suspected pericarditis/myocarditis	2	0

Twenty-five men, 25 women, age range 29 to 64 years (mean 49).

AVR = abnormal vasodilator reserve (as determined by coronary flow study, see text); NVR = normal vasodilator reserve.

TABLE II Electrocardiograms in Study Patients

	Patients (n)
Electrocardiograms at rest	50
Normal	38
Abnormal	
Q waves	2
Conduction abnormalities	3
Preexcitation	1
ST-T–wave abnormalities	6
Electrocardiograms during chest pain	29
No change	24
T-wave changes	5
Electrocardiograms during exercise	50
Greater than 1 mm horizontal or downslope ST depression	2

TABLE III Results of Diagnostic Angiographic Studies Performed in 50 Study Patients

	Patients (n)
Coronary arteriography	
Normal coronary arteries	41
<30% luminal narrowing of any coronary artery	9
Contrast ventriculography	
Normal left ventricle	39
Wall motion abnormalities	11

results of our first study of 16 patients were reported previously.[4] Ten of the patients were believed, on the basis of history and physical examination, to have musculoskeletal or other noncardiac cause for their chest pain. This determination was made before the patient's entry into the study. The remaining 40 patients gave histories consistent with ischemic cardiac pain.

A minority of patients were insulin-requiring diabetic, smoking or hypertensive subjects (Table I). Most patients were in good general health until adult life when chest pain was first experienced. Although these patients were often reassured as to the benign nature of their chest pain on the basis of previous noninvasive and invasive testing, most considered their pain to be cardiac in origin, significantly debilitating and warranting further evaluation. The majority of patients had electrocardiograms (ECGs) obtained during episodes of chest pain—none showed ≥1 mm ST-segment shifts, and most remained unchanged (Table II). Six patients were reported by their referring physician to have had myocardial infarctions. A careful physical examination was performed before the study, with attention to musculoskeletal chest wall tenderness.[5] All patients underwent bicycle exercise testing using a National Institutes of Health protocol[6]; 2 had >1 mm horizontal or downsloping ST depression. The remaining patients had nonspecific ST-T–wave changes or no change in 12-lead recording during and after exercise (Table II). M-mode ECGs were performed in all patients and 2-D ECGs in the majority: none had evidence of hypertrophic cardiomyopathy and 3 had mitral valve prolapse.

Medications were discontinued in all patients and 48 hours or more later each patient underwent cardiac catheterization. Routine diagnostic coronary arteriography, using multiple angulated views, was first performed. Although in our previous study[4] some patients were included who had significant narrowing of a coronary artery other than the left anterior descending coronary artery, only patients with normal epicardial arteries, or minor wall placquing, were included in the present study (Table III). An 8Fr pigtail fluid-filled (12 patients) or micromanometer-tipped (Millar Instruments) catheter was positioned in the left ventricle of the last 24 patients studied. A Swan-Ganz thermodilution balloon-tipped catheter (Edwards Laboratories) was positioned in a peripheral pulmonary artery in 41 patients. A thermodilution pacing catheter[7] (Elecath Corporation) was introduced through the right internal jugular vein and advanced through the coronary sinus into the great cardiac vein (GCV), which drains approximately 90% of the anterior myocardial circulation (left anterior descending and diagonal branches).[8,9] Catheter stability was maintained throughout the entire study by frequent position checks using fluoroscopy and by repeat baseline rest flow determinations. A 20-gauge Teflon catheter was placed in the left brachial artery for blood pressure monitoring and recording.

The study protocol was initiated at least 30 minutes after use of contrast material so that any effects of dye on coronary blood flow or metabolism would subside.[10] The present series consists of 50 consecutive patients in whom GCV flow measurements were successfully obtained using the protocol described later. GCV flow (50 patients), lactate (50 patients) and oxygen content (32 patients) were determined at rest, as were measurements of cardiac index (CI) (41 patients), mean pulmonary artery wedge pressure (PCW) (41 patients), and left ventricular end-diastolic pressure (LVEDP) (24 patients). Pacing through the coronary sinus catheter was initiated at a heart rate (HR) of 100 beats/min, and increased by 10 beats/min increments at 1-minute intervals up to a HR of 150 beats/min. In 13 patients, atropine, 0.5 to 1.0 mg, was administered intravenously to achieve a HR of 150 beats/min. In 2 patients, pacing was terminated at a HR of 130 beats/min. At the final HR, repeat GCV flow and lactate, arterial and GCV oxygen content, and CI measurements were made. Pacing was then terminated and LVEDP and PCW were monitored after pacing in 24 patients for 10 seconds and averaged, eliminating the first 4 postpacing beats. Arteriography of the left coronary artery was performed in 2 views 90° apart for quantitative measurement of epicardial coronary artery caliber.

After a rest period of 20 minutes to allow any contrast media-induced alteration of coronary blood flow or metabolism to subside, we again measured baseline GCV flow, lactate, arterial and GCV oxygen contents, and PCW and LVED pressures. Repeat baseline measurements were not made in Patient 14, because of persistent atropine-induced tachycardia. Ergonovine, 0.15 mg, was then administered intrave-

TABLE IV Hemodynamic Data During Control Study

Patient	Age (yr) & Sex	Rest HR (beats/min)	Rest BP (mm Hg)	Rest (GCV-F (ml/min)	Rest CR (mm Hg/ml/min)	Pacing HR (beats/min)	Pacing BP (mm Hg)	Pacing GCV-F (ml/min)	Pacing % ΔF	Pacing CR (mm Hg/ml/min)	Pacing % ΔR
No Chest Pain											
Patients thought to have noncardiac pain on history											
1	55M	74	93	96	0.97	150	99	156	63	0.63	−35
2	57F	80	112	68	1.65	150	118	126	85	0.94	−43
3	57M	98	100	52	1.92	150	102	86	65	1.19	−38
4	49M	55	108	54	2.00	150*	100	128	137	0.78	−61
5	58F	65	85	70	1.21	150*	90	136	94	0.66	−46
6	36F	78	96	94	1.02	150	94	170	81	0.55	−46
7	58M	77	87	105	0.83	150	90	163	55	0.55	−34
8	47M	76	90	57	1.58	150	90	88	54	1.02	−35
9	56F	65	76	42	1.81	150	90	100	138	0.90	−50
10	29F	63	90	57	1.58	150	95	94	65	1.01	−36
Patients thought to have possible cardiac pain on history											
11	48F	54	98	74	1.32	150	107	174	135	0.61	−54
12	38M	68	75	49	1.53	150	81	96	96	0.84	−45
13	47M	81	95	62	1.53	150	108	117	89	0.92	−40
14	32F	74	110	69	1.59	150*	120	130	74	0.92	−42
15	50F	78	110	63	1.75	150	122	121	92	1.01	−42
16	41M	68	112	89	1.26	150*	114	156	75	0.73	−42
17	60F	65	95	74	1.28	150*	90	139	88	0.65	−49
18	61F	80	104	34	3.06	150	124	75	121	1.65	−46
19	30M	72	80	69	1.16	150*	85	126	83	0.68	−41
20	47M	67	86	58	1.48	150	100	113	95	0.89	−40
21	42M	78	114	73	1.56	150	112	131	80	0.86	−45
22	50M	67	84	64	1.31	150*	85	120	88	0.71	−46
23	54F	70	76	74	1.03	150	86	122	65	0.71	−31
24	42F	85	123	58	2.12	150	120	90	55	1.33	−37
25	31M	78	97	80	1.21	150	96	144	80	0.67	−45
26	46M	82	115	69	1.67	150	120	126	83	0.95	−43
Mean		73	97	68	1.52	150	102	124	86	0.86	−43
± SD		10	14	16	0.45	0	14	27	24	0.25	7
Developing Chest Pain											
27	47F	75	82	42	1.95	130	93	63	50	1.48	−24
28	53M	72	103	49	2.10	150	108	63	29	1.71	−19
29	57M	74	85	66	1.29	150	90	124	88	0.73	−43
30	54F	92	85	70	1.21	150	90	82	17	1.10	−9
31	55F	77	122	46	2.65	150*	125	66	43	1.89	−29
32	58F	68	100	68	1.47	150*	118	106	56	1.11	−25
33	43M	74	97	57	1.70	150	109	60	5	1.82	+7
34	48M	92	89	41	2.17	150	93	50	22	1.86	−14
35	37M	69	88	89	0.99	150	98	131	47	0.75	−24
36	52F	89	117	57	2.05	150	120	88	54	1.36	−34
37	54F	92	130	97	1.34	150	150	118	22	1.27	−5
38	62F	78	115	78	1.47	150	120	88	13	1.36	−8
39	49M	88	105	82	1.28	150	106	110	34	0.96	−25
40	61M	80	116	96	1.15	150*	140	132	38	1.06	−8
41	44F	80	90	98	0.87	150	100	145	48	0.69	−21
42	50M	75	74	79	0.94	130*	82	114	44	0.72	−23
43	64F	71	79	71	1.32	150	118	95	34	1.24	−6
44	46F	79	88	61	1.44	150*	96	87	43	1.10	−24
45	60F	76	94	66	1.42	150	120	79	20	1.52	+7
46	39M	72	98	70	1.40	150	106	88	26	1.21	−14
47	48M	100	105	92	1.14	150	104	132	43	0.79	−31
48	36F	56	75	80	0.94	150	90	101	26	0.89	−5
49	52M	90	108	98	1.10	150	107	105	7	1.02	−7
50	56F	84	118	82	1.43	150*	120	116	42	1.03	−28
Mean		79	99	72	1.45	148	109	98†	36†	1.20†	−17†
± SD		10	16	18	0.45	6	17	26	18	0.37	12

p values determined comparing patients developing versus those not developing chest pain.
* Atropine.
† $p < 0.001$.
BP = mean arterial blood pressure; CR = coronary resistance; GCV-F = great cardiac vein flow; HR = heart rate; % ΔF = percent change in GCV-F from rest; % ΔR = percent change in CR from rest; SD = standard deviation.

nously to 46 patients (the remaining 4 patients participated in other studies). Although the patients were aware that ergonovine would be administered sometime during the study, the actual administration of the drug was performed without their knowledge. Repeat measurements of GCV flow were performed at 45 seconds and immediately thereafter pacing was initiated at a HR of 130 beats/min. Pacing was then increased to 150 beats/min with repeat measurements as described for the control study, after which time pacing was discontinued, and LVED and PCW pressures were measured for 10 seconds. Arteriography was then performed (approximately 4 minutes after administration of ergonovine) in the same views as the control study. The majority of patients received an additional 0.25 mg of ergonovine with repeat arteriograms.

Measurement analysis: The thermodilution method for determining GCV flow has been described previously.[7,9–11] Coronary resistance was calculated as the mean arterial pressure divided by GCV flow. Coronary sinus flow measurements were not recorded because of concern for possible right atrial reflux during pacing.[12] Leads I, II and III were recorded during the studies for the first 16 patients, and leads I, AVF and V_5 during the studies for the remaining 34 patients. Lactate samples were obtained from the artery and GCV and collected in tubes containing potassium oxalate and sodium fluoride for red blood cell glycolytic inhibition. The samples were immediately centrifuged at 5,000 rpm for 10 minutes at 4°C and the serum was decanted and refrigerated in the catheterization laboratory. Specimens were analyzed on a Dupont automatic clinical analyzer by a modification of the technique of Marbach and Weil.[13] Lactate consumption was calculated as GCV flow multiplied by the difference between arterial and GVC lactate concentrations. Blood oxygen content was measured by a Lex-O_2-Con-K oxygen analyzer (Lexington Instruments) with frequent duplicate determinations and at least 1 change of scrubber gas during the course of the study. Arterial-venous oxygen (AVO_2) difference represented arterial minus GCV oxygen content, and myocardial oxygen consumption ($M\dot{V}O_2$) was determined by the product of GCV flow and AVO_2 difference, representing oxygen consumption in the anterior left ventricle and interventricular septum.

Arteriograms of the coronary arteries for quantitative measurement were always obtained in 2 views 90° apart, usually 60° left anterior oblique and 30° right anterior oblique, using Siemens-Elema equipment with C-Arm so that the patient was not moved during the study. The developed films were projected on a Vanguard cine-projector at approximately 3× magnification. In 14 patients, 10 × 12 cm cut films were obtained at 2 films/s for 3 seconds. For either angiographic technique, coronary artery luminal diameter was measured using calipers at multiple positions along the proximal, mid and distal epicardial arteries. Measurements were made by 2 observers without knowledge of the catheterization results, using the known dimensions of the 8Fr Judkins left coronary catheter as a reference measurement. Care was taken to use frames in which the region of interest was centered on the screen or cut film to avoid magnification and other distortion artifacts. Measurements were made at identical points in the 2 views, using branch arteries as references, and were averaged.

Data were analyzed using Student's t test for paired and unpaired data with a probability value <0.05 considered significant. All grouped data are reported as mean ± standard deviation.

Results

Control study: The mean baseline GCV flow for the control study (Table IV) was similar to that of previously published studies using the thermodilution method.[7,9,14,15] During the control pacing study, 2 symptomatic responses were elicited; 24 patients had their typical chest discomfort, and 26 reported either no chest discomfort or pacing-related chest sensations that were clearly different from their typical spontaneously occurring chest pain. Table IV contains the heart rate, mean blood pressure, GCV flow and calculated coronary resistance at rest and during pacing at a heart rate of 150 beats/min (130 beats/min in 2 patients). Figure 1A displays the absolute GCV flow at rest, during intermediate pacing (130 beats/min in most patients) and final pacing in all 50 patients. Those patients not having chest pain had a significantly higher flow response (124 ± 27 ml/min) than those patients having their typical chest discomfort (98 ± 26 ml/min, $p <0.001$). Calculated coronary resistance (Fig. 1B) decreased less in the 24 patients having their typical chest discomfort, a difference that was significant at both intermediate (1.25 ± 0.43 versus 1.03 ± 0.22 mm Hg/ml/min, $p <0.025$) and final pacing rate (1.20 ± 0.37 versus 0.86 ± 0.25 mm Hg/ml/min, $p <0.001$).

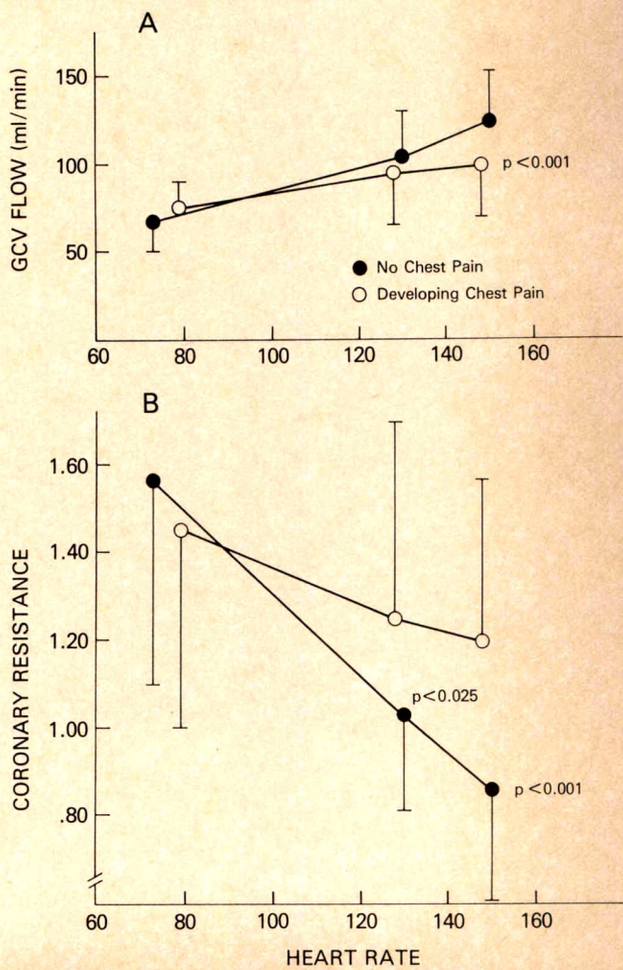

FIGURE 1. Great cardiac vein (GCV) flow (**A**) and calculated coronary resistance (**B**) during control study in 50 patients at rest and during intermediate and high-paced heart rates. **Closed circles** represent group without chest pain; **open circles** represent group having their typical chest pain during pacing. Circles represent mean values ± standard deviation.

Because the portion of anterior circulation coronary flow drained by the GCV may vary from person to person[8] (although it averages approximately 90% of left anterior descending flow), the percent change in GCV flow and coronary resistance from rest to maximal pacing was also calculated, so that each person served as his or her own control (Table IV). Flow increased less in those patients having their typical chest discomfort during pacing (36 ± 18% versus 86 ± 24%, p <0.001) than it did in the patients without chest pain (Table IV, Fig. 2). Likewise, coronary resistance decreased less in those patients having chest pain (−17 ± 12% versus −43 ± 7%, p <0.001) that it did in the patients without chest pain. Lactate consumption at a HR of 150 beats/min (Fig. 3) was significantly lower in those patients experiencing chest pain compared with those without chest pain (28.3 ± 21.5 versus 51.3 ± 35.8 mM·ml/min, p <0.001) because lactate consumption increased less or actually decreased during pacing. During pacing, AVO_2 difference decreased significantly (12.4 ± 1.7 at rest to 11.6 ± 1.5 ml O_2/100 ml during pacing, p <0.001) in those patients without chest pain, whereas the AVO_2 difference was unchanged in those patients having chest pain (11.6 ± 1.3 at rest to 11.6 ± 1.7 ml O_2/100 ml during pacing), as demonstrated in Figure 4. Despite the significant difference in GCV flow between the 2 groups, the $M\dot{V}O_2$ and systolic blood pressure-heart rate product were not significantly different at maximal pacing (Table V).

The cardiac index at rest was similar in both groups and did not change during peak pacing (Fig. 4). The LVEDP and PCW at rest in the patients without chest pain (11 ± 3 and 7 ± 3 mm Hg, respectively, Fig. 5) were essentially unchanged after pacing (12 ± 4 and 9 ± 3 mm Hg). In contrast, although the LVEDP and PCW were similar at rest (9 ± 5 and 7 ± 4 mm Hg, respectively), those patients having chest pain during pacing had a significant increase in LVEDP (14 ± 5 mm Hg, p <0.001) and PCW (11 ± 5 mm Hg, p <0.001) after pacing compared with rest measurements. In addition, the change in LVEDP from rest to postpacing was significantly greater in the chest pain group that the nonchest pain group (5 ± 2 versus 1 ± 2 mm Hg, p <0.001). No significant ST-segment depression or elevation was noted in any patient after pacing.

Ergonovine study: After a period of at least 20 minutes after the control study, repeat baseline mea-

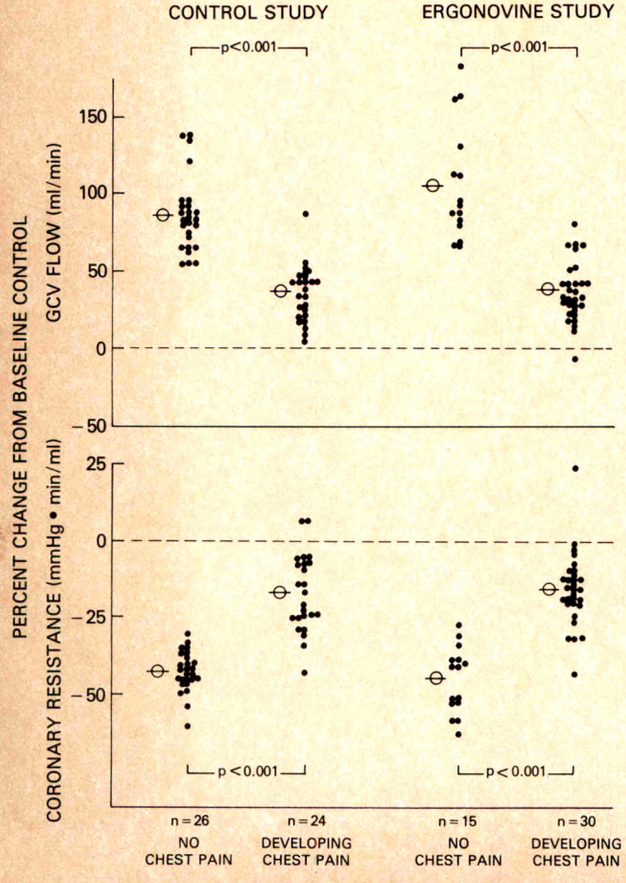

FIGURE 2. Percent change in great cardiac vein (GCV) flow and coronary resistance during pacing from rest baseline level during control and ergonovine studies. **Large circles with bars** indicate mean value.

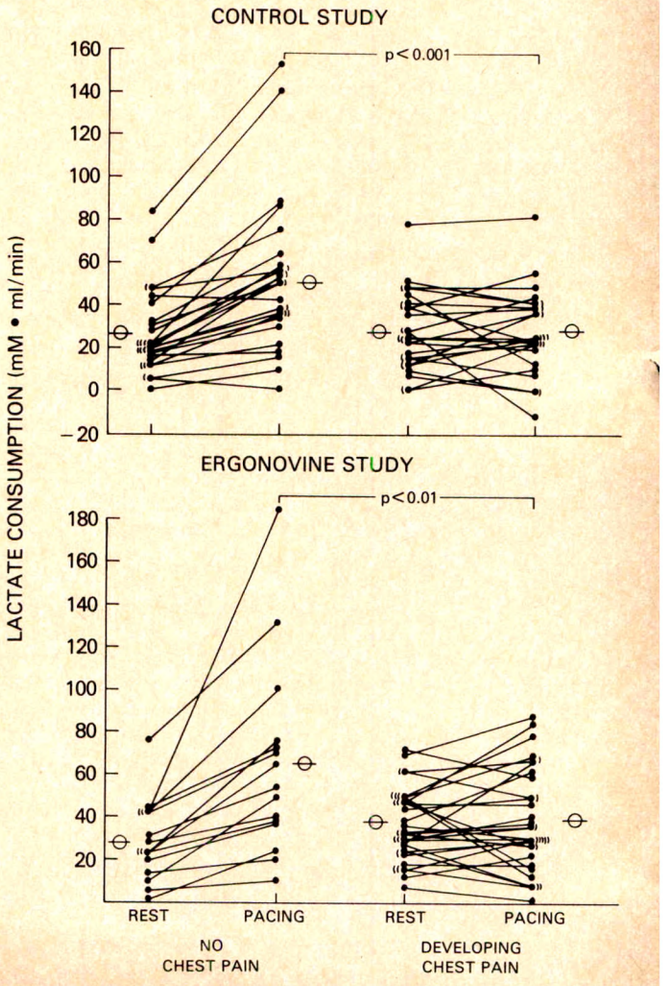

FIGURE 3. Lactate consumption ([arterial − great cardiac vein lactate concentration] × great cardiac vein flow) at rest and during maximal paced heart rate during control and ergonovine studies. **Large circles with bars** indicate mean value.

TABLE V Anterior Circulation Myocardial Oxygen Consumption During Control and Ergonovine Studies

Study Protocol	Chest Pain	N	Rest GCV Flow (ml/min)	Rest $M\dot{V}O_2$	Rest HR × SBP Product	Pacing GCV Flow	Pacing $M\dot{V}O_2$	Pacing HR × SBP Product
Control	No	19	68 ± 18	8.4 ± 2.6	9.4 ± 2.6	122 ± 27	14.1 ± 3.9	18.3 ± 2.5
	Yes	13	80 ± 12	9.2 ± 1.9	11.0 ± 3.6	106 ± 20*	12.4 ± 3.4	19.8 ± 3.8
Ergonovine	No	9	68 ± 20	8.6 ± 3.2	10.3 ± 1.7	136 ± 40	15.9 ± 5.8	19.5 ± 2.1
	Yes	18	74 ± 15	8.9 ± 2.2	10.2 ± 3.7	102 ± 27†	13.1 ± 4.1	21.1 ± 3.3

* $p < 0.05$ versus control study GCV flow during pacing, no chest pain group.
† $p < 0.01$ versus ergonovine study GCV flow during pacing, no chest pain group.
GCV flow = great cardiac vein flow; HR = heart rate; $M\dot{V}O_2$ = anterior circulation oxygen consumption (ml O_2/min = AVO_2 diffference × GCV flow); SBP = systolic blood pressure.

surements were obtained. After administration of ergonovine, 0.15 mg intravenously, to 46 patients, 1 patient had chest pain before initiation of pacing and 30 other patients had their typical chest pain during subsequent pacing, including 13 patients who had no chest pain during the control study. Fifteen patients had no chest pain after ergonovine at rest, or during pacing, including 2 patients who had chest pain during the control study. There was no significant difference in baseline control values of HR, blood pressure, GCV flow or coronary resistance between the 2 groups (Table VI), nor was there significant change in these parameters from baseline values in the control study.

After administration of ergonovine, but before pacing, the group that subsequently had chest pain had a significant increase in coronary resistance and no change in GCV flow, whereas coronary resistance decreased and GCV flow increased in those never having chest pain after ergonovine (Fig. 6). The patient with chest pain before pacing (Patient 29) had the greatest increase in coronary resistance and decrease in GCV flow of any patient (Table VI). No ST-segment shift was observed on monitored leads in any patient.

During peak pacing after ergonovine administration, those patients having their typical chest pain had a lower absolute GCV flow (102 ± 28 versus 138 ± 31

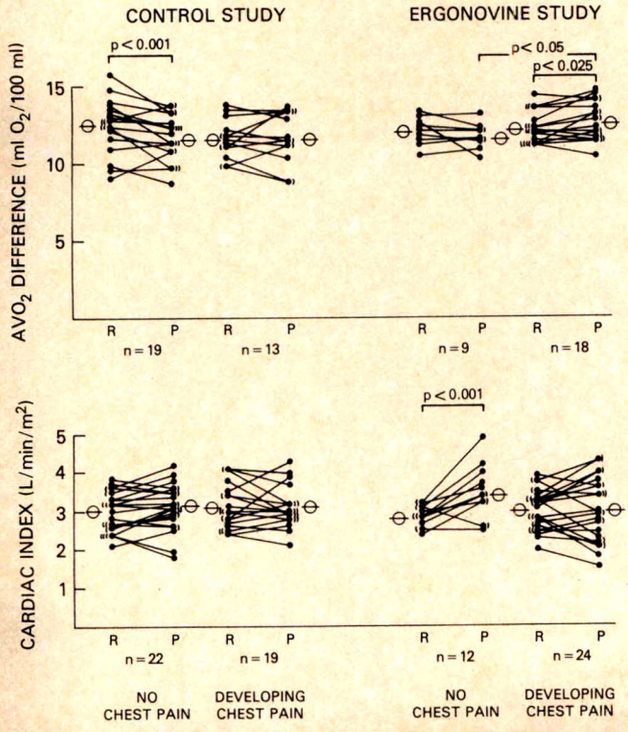

FIGURE 4. Arterial — great cardiac vein oxygen (AVO_2) difference and cardiac index at rest (R) and during maximal paced heart rate (P) in patients with and without chest pain during control and ergonovine studies.

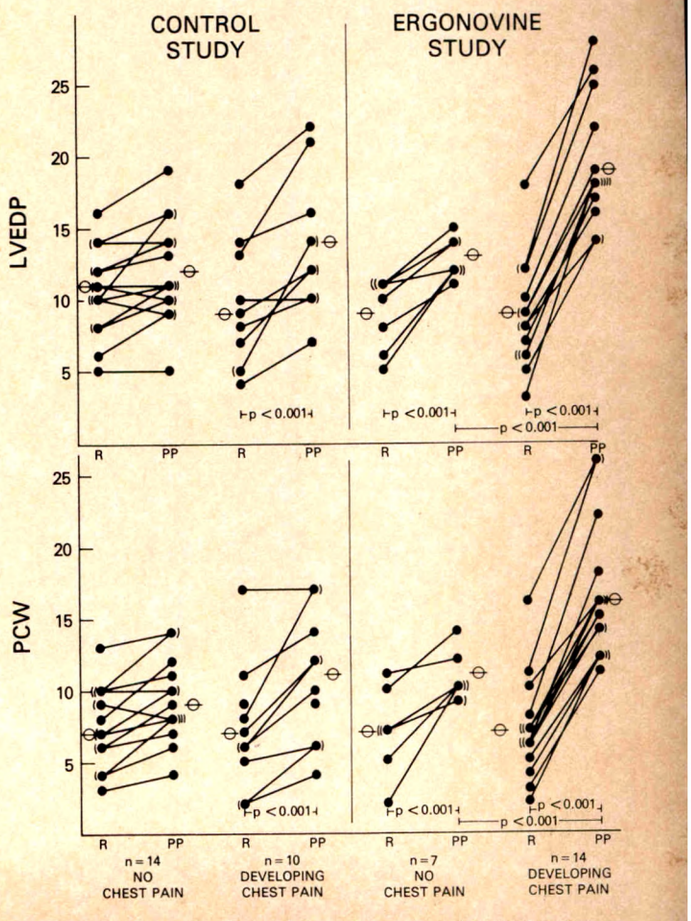

FIGURE 5. Left ventricular end-diastolic pressure (LVEDP) and mean pulmonary artery wedge pressure (PCW) at rest (R) and after termination of maximal pacing (PP), averaged over 10 seconds, eliminating first 4 beats, during control and ergonovine studies.

TABLE VI Hemodynamic Data During Ergonovine Study

Patient	Rest				Ergonovine Rest						Ergonovine Pacing					
	HR (beats/min)	BP (mm Hg)	GCV-F (ml/min)	CR (mm Hg/ml/min)	HR (beats/min)	BP (mm Hg)	GCV-F (ml/min)	%ΔF	CR (mm Hg/ml/min)	%ΔR	HR (beats/min)	BP (mm Hg)	GCV-F (ml/min)	%ΔF	CR (mm Hg/ml/min)	%ΔR
No Chest Pain																
1	68	89	85	1.05	71	94	84	−1	1.12	7	150	97	141	66	0.69	−34
2	78	125	65	1.92	92	130	105	62	1.24	−35	150	122	128	97	0.95	−51
3	78	110	48	2.29	83	110	48	0	2.29	0	150	105	93	94	1.12	−51
4	79	119	58	1.90	83	115	58	0	1.98	4	150*	119	153	164	0.78	−58
5	93	85	68	1.25	94	95	81	19	1.17	−6	150	95	178	162	0.53	−58
6	80	90	82	1.10	84	92	84	2	1.10	0	150	100	189	131	0.53	−52
7	102	92	113	0.81	103	96	144	27	0.67	−17	150	105	188	66	0.56	−31
8	73	90	59	1.53	74	92	65	10	1.42	−7	150	103	108	83	0.95	−38
9	66	88	56	1.57	68	92	58	4	1.59	1	150	110	120	114	0.92	−41
10	72	80	63	1.27	63	96	84	33	1.14	−10	150	98	106	68	0.93	−27
21	83	114	67	1.70	84	116	66	−2	1.76	−4	150	116	143	113	0.81	−52
24	83	120	53	2.26	84	125	61	15	2.05	−9	150	135	96	81	1.41	−38
25	83	106	83	1.28	83	110	91	10	1.21	−6	150	119	156	88	0.76	−41
33	78	108	72	1.50	77	110	85	18	1.29	−17	150	123	136	89	0.90	−40
34	67	91	46	1.98	82	98	49	7	2.00	1	150	97	131	183	0.74	−63
Mean	79	101	68	1.56	82	105	78	14	1.47	−7	150	110	138	107	0.84	−45
± SD	10	15	17	0.44	10	13	25	17	0.46	11	0	12	31	38	0.23	11
Developing Chest Pain																
11	72	115	126	0.91	72	120	117	−7	1.03	13	150	113	163	29	0.69	−24
12	82	85	63	1.35	73	90	103	63	0.87	−36	150*	107	90	43	1.19	−12
13	76	100	73	1.37	82	104	65	−11	1.60	17	150	115	104	43	1.11	−20
14											150	140	103		1.36	
15	76	108	61	1.77	83	112	63	3	1.78	1	150	118	93	53	1.27	−28
16	85	106	87	1.22	77	108	84	−4	1.29	7	150*	122	147	69	0.83	−32
17	75	102	79	1.29	82	115	82	4	1.40	9	150	117	131	66	0.89	−31
18	84	95	43	2.21	78	100	41	−5	2.44	10	150	130	59	32	2.20	−1
19	88	86	78	1.10	85	90	82	5	1.10	0	150	94	98	26	0.96	−13
20	82	86	56	1.54	84	86	48	−14	1.79	16	150	98	93	66	1.05	−32
22	85	90	63	1.43	90	98	56	−11	1.75	22	150	108	84	33	1.29	−10
23	67	85	64	1.33	70	86	86	34	1.00	−25	150	88	120	88	0.73	−45
26	95	120	69	1.74	94	128	75	9	1.71	−2	150	120	77	12	1.56	−10
27	58	90	44	2.05	70	102	61	39	1.67	−19	120	121	74	68	1.64	−20
28	70	97	47	2.06	70	107	47	0	2.28	11	150	112	64	36	1.75	−15
29	63	80	80	1.00	65	90	63	−21	1.43	43	150	99	121	51	0.82	−18
30	94	91	67	1.36	92	99	65	−3	1.52	12	150	100	86	28	1.16	−15
31	96	108	72	1.50	92	115	66	−8	1.74	16	150*	115	85	32	1.21	−19
32	94	115	71	1.62	93	125	82	16	1.52	−6	150	123	92	30	1.34	−17
35	72	94	96	0.98	65	105	88	−8	1.19	21	150*	106	137	43	0.77	−21
36	80	130	63	2.06	80	145	77	22	1.88	−9	140	140	77	22	1.82	−12
37	82	130	75	1.73	85	150	63	−16	2.38	38	150	168	89	19	1.89	−9
40	100	108	104	1.04	96	125	94	−10	1.33	28	150*	144	149	43	0.97	−7
41	73	90	91	0.99	78	90	82	−10	1.10	11	150	105	126	39	0.83	−16
42	94	77	80	0.96	97	90	74	−8	1.22	27	130*	90	98	23	0.92	−4
43	75	104	86	1.21	73	108	95	11	1.14	−6	150	122	81	−6	1.51	+25
44	93	88	62	1.42	86	96	68	10	1.41	−1	140	104	83	34	1.25	−12
45	95	108	59	1.83	95	112	56	−5	2.00	9	150	120	68	15	1.77	−3
46	82	97	67	1.45	78	105	65	−3	1.62	12	150	112	96	43	1.17	−19
47	90	100	123	0.81	95	105	129	5	0.81	0	150	108	165	34	0.66	−19
50	105	125	94	1.33	115	140	98	4	1.43	8	150	138	112	19	1.23	−8
Mean	83	100	75	1.42	83	108	76	3	1.51	8	148	116	102†	38†	1.22†	−16†
± SD	12	14	20	0.38	11	17	20	18	0.42	17	7	17	28	20	0.39	12

p values determined comparing patients developing versus those not developing chest pain. * Atropine. † $p < 0.001$. Abbreviations as in Table IV.

ml/min, $p < 0.001$) and less of an increase in flow (38 ± 20% versus 107 ± 38%, $p < 0.001$) than those patients never having pain (Table VI, Fig. 2). Likewise, those patients having chest pain had a higher coronary resistance (1.22 ± 0.39 versus 0.84 ± 0.23 mm Hg/ml/min, $p < 0.001$), and less of a decrease in coronary resistance (−16 ± 12% versus −45 ± 11%, $p < 0.001$) compared with those patients never having chest pain. None of the 10 patients (Table IV) believed prospectively to have noncardiac pain had their typical chest pain during the ergonovine study.

Lactate consumption during peak pacing (Fig. 3) was significantly less in those patients having chest pain (39.2 ± 23.6 versus 65.3 ± 46.3 mM·ml/min, $p < 0.01$) compared with those patients without chest pain. AVO_2 difference decreased slightly (12.1 ± 0.9 at rest to 11.6 ± 1.1 ml O_2/100 ml during pacing, not significant) in those patients without pain (Fig. 4). In contrast, AVO_2 difference widened significantly (12.2 ± 1.1 at rest to 12.5 ± 1.3 ml O_2/100 ml during pacing, $p < 0.025$) in those patients with chest pain after ergonovine. During peak pacing, those patients having pain had a greater AVO_2 difference compared with those patients without pain (12.5 ± 1.3 versus 11.6 ± 1.0 ml O_2/100 ml, $p < 0.05$). Despite the significant difference in GCV flow between the 2 groups during maximal pacing, the pressure-rate product and $M\dot{V}O_2$ were not significantly different between the 2 groups (Table V).

The CI increased significantly during peak pacing after ergonovine in the group without chest pain (2.8 ± 0.3 at rest to 3.4 ± 0.7 liters/min/m^2 during pacing, $p < 0.001$) (Fig. 4) but was unchanged in the group with chest pain. After pacing, the LVEDP and PCW were significantly higher in the chest-pain group (19 ± 4 mm Hg, $p < 0.001$, and 16 ± 4 mm Hg, respectively, $p < 0.001$) (Fig. 5) compared with the no-chest-pain group (13 ± 2 and 11 ± 2 mm Hg). The increase in LVEDP (11 ± 3 versus 5 ± 2 mm Hg, $p < 0.001$) and PCW (9 ± 3 versus 4 ± 2 mm Hg, $p < 0.001$) from rest to postpacing was likewise significantly greater in the chest-pain group. Significant ST-segment depression (≥1 mm) after pacing was noted in 2 patients having chest pain.

Selective coronary arteriography performed immediately after pacing (approximately 4 minutes after ergonovine administration) showed no focal spasm and only minimal epicardial coronary artery luminal narrowing (−5 ± 7% proximal, −6 ± 9% mid, −4 ± 11% distal left anterior descending) compared with control arteriograms. Further administration of ergonovine in the majority of patients up to a cumulative dose of 0.4 mg produced <20% epicardial artery narrowing and no focal spasm.

Dynamic coronary vasoconstriction: Thirty-one patients had their typical chest discomfort during the ergonovine study, including 13 patients who had no chest pain during the control pacing study. Vasoconstriction of the coronary microcirculation was suggested by several observations. First, coronary resistance actually increased and GCV flow decreased in the patient having chest pain at rest after ergonovine infusion; these changes were the largest of any patient in the study and occurred without significant epicardial coronary artery luminal narrowing. In the remaining 30 patients with chest pain, coronary resistance increased significantly after ergonovine administration without epicardial coronary artery vasoconstriction, whereas it actually decreased in those patients never having chest pain. Second, during pacing at a HR of 150 beats/min, coronary resistance was higher (1.04 ± 0.34 mm Hg/ml/min, control study versus 1.22 ± 0.40 mm Hg/ml/min, erogonovine study, $p < 0.001$) and GCV flow was lower (111 ± 27 ml/min, control study versus 102 ± 28 ml/min, ergonovine study, $p < 0.001$) during ergonovine infusion in the 31 patients having chest pain, when compared with the control study at the same paced HR. This increase in resistance could not be ascribed to autoregulatory mechanisms responding to a lower $M\dot{V}O_2$, as the systolic blood pressure and HR product, an index of $M\dot{V}O_2$, was actually higher at maximal HR during the

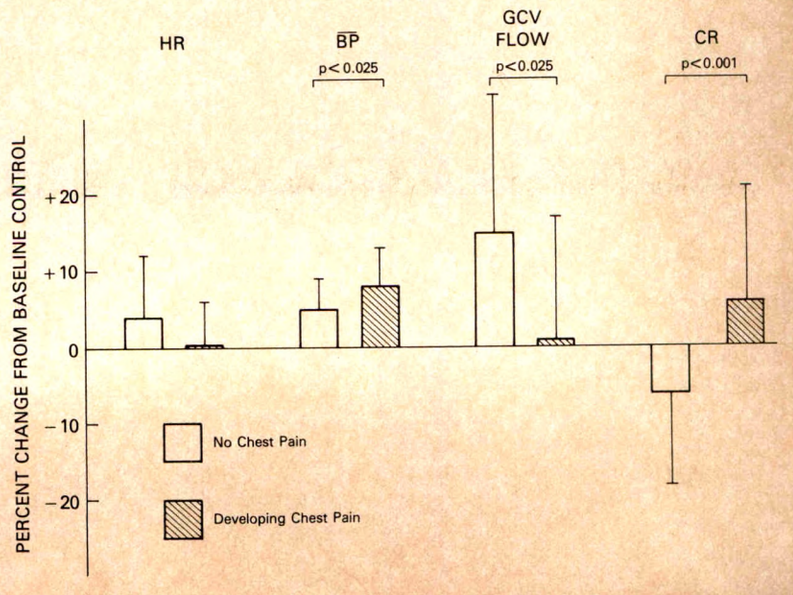

FIGURE 6. Percent change from baseline control after administration of ergonovine in heart rate (HR), mean blood pressure (BP), great cardiac vein (GCV) flow and coronary resistance (CR).

ergonovine study ($19.6 \pm 3.6 \times 10^3$, control study versus $20.6 \pm 3.3 \times 10^3$, ergonovine study, $p < 0.001$). This was confirmed by direct measurements of $M\dot{V}O_2$ in a subgroup of patients having chest pain after ergonovine: $M\dot{V}O_2$ was not lower at maximal paced HR during the ergonovine study (13.5 ± 3.7 ml O_2/min during control pacing versus 13.1 ± 4.1 ml O_2/min, not significant). Because coronary resistance actually increased in this group of patients, it appears that the changes we observed were due to an ergonovine-induced coronary vasoconstrictor response. That vasoconstrictor stimuli overrode autoregulatory influences is suggested by the fact that constriction occurred not only in the face of an increase in oxygen demand, but during myocardial ischemia, as evidenced by abnormal lactate metabolism, widening of the AVO_2 difference and elevation of the postpacing LVEDP.

Discussion

This study demonstrates that the chest pain had by many patients previously considered to have "normal" coronary arteries, and therefore noncardiac chest pain, may in fact be due to myocardial ischemia induced by abnormalities of the coronary microcirculation or arteries too small to be imaged by current arteriographic techniques. That the chest pain is ischemic in origin is suggested by several findings. When patients had their chest pain during pacing, a limitation in coronary blood flow increase occurred similar to that found in patients with obstructive coronary artery disease.[14] The pain and abnormal flow responses were associated with diminished lactate consumption and elevated postpacing LVEDP. These changes are characteristic of an ischemic response, reflecting alterations in aerobic metabolism[16,17] and ventricular compliance.[18] That the abnormal flow and resistance changes are due to inappropriate vasodilator reserve, or constriction of small coronary arteries or arterioles, is indicated by the fact that no significant alterations in epicardial coronary artery caliber were noted that could explain the increased resistance and inadequate flow responses.

The evidence favoring the concept that the abnormal vasodilator reserve exhibited by our patients produces myocardial ischemia must be critically assessed, because we are ascribing to ischemia the basic pathophysiologic mechanism responsible for the clinical syndrome presented by these patients. In this regard, although the decreased lactate consumption observed during pacing is less convincing evidence of ischemia than frank lactate production, the decrease in consumption probably represents a point on the spectrum of lactate metabolism ranging from appropriate increases in lactate consumption in response to increases in $M\dot{V}O_2$, to ischemia-induced lactate production.[16,17] Assessment of lactate metabolism from myocardial venous drainage also necessarily introduces sampling errors if the myocardium is not uniformly ischemic.[17] If the abnormal microcirculatory responses to pacing and ergonovine are diffuse or "patchy" in distribution, or primarily endocardial versus epicardial in location, the regional venous drainage may convey an admixture of normal and abnormal lactate responses, especially if the overall mass of ischemic myocardium is small. In addition, the sensitivity of lactate production assessment in detecting ischemia even in patients with significant obstructive coronary artery disease is modest at best.[19]

In contrast to the ischemic responses observed in the patients having chest pain, those patients not having chest pain during the control study achieved higher coronary blood flow responses to pacing, increased their lactate consumption, and had only minimal increases in LVEDP. The higher flow could not be ascribed to greater oxygen demands, as both the systolic blood pressure-HR product, an estimate of $M\dot{V}O_2$, and directly measured $M\dot{V}O_2$, were comparable to the values measured in patients with chest pain.

Further evidence favoring the concept that the chest pain our patients had was due to myocardial ischemia is suggested by our recent study, using radionuclide gated blood-pool imaging, which demonstrated that three quarters of our patients with abnormal vasodilator reserve had abnormalities of left ventricular function, either at rest or during exercise.[20]

Ergonovine infusion resulted in several interesting observations. First, 1 patient (Patient 29) had chest pain at rest associated with the greatest decrease in GCV flow and increase in coronary resistance of any patient in the study, and in another patient (Patient 43) coronary resistance actually increased during subsequent pacing, a change that was not accompanied by significant changes in epicardial coronary artery luminal diameter. Second, as a group, coronary resistance at rest actually increased in response to ergonovine in those patients who would have their typical pain during subsequent pacing. This was just the opposite of the appropriate response to the ergonovine-induced increase in arterial pressure, as exhibited by those patients never having pain in the ergonovine study—a decrease in coronary resistance and increase in GCV flow.

Although other studies have also suggested that some patients with chest pain and normal epicardial coronary arteries may have an abnormal small vessel response to ergonovine,[21–23] no data were obtained during hemodynamic stress and ischemia was not documented. This is extremely important from a pathophysiologic point of view. Thus, we found that when compared with the results of pacing in the control study, exacerbation of flow and resistance abnormalities occurred in those patients in whom pacing and ergonovine infusion actually resulted in chest pain (with associated metabolic and hemodynamic findings compatible with ischemia). Additionally, ergonovine and pacing precipitated an ischemic response in 13 patients who had a normal response to pacing during the control study. Normally, coronary arterioles act as the primary regulators of coronary blood flow; they dilate as myocardial oxygen demands increase so as to tightly couple myocardial oxygen supply and demand. In the patients with chest pain in this study, autoregulation of coronary blood flow was abnormal, such that vasoconstriction or inadequate vasodilation occurred even in the presence of myocardial ischemia. The abnormality appears to be dynamic, in that vasoconstrictor stimuli unmask or exacerbate this condition, a finding that may explain the mecha-

nism of resting and exertional chest pain with variation in anginal threshold, which was a clinical feature usually noted in these patients.

Limitations of study: The present study contained no true asymptomatic control subjects (normal volunteers), because in our judgment ethical considerations prohibited participation of such a population in an extensive invasive study that carried a risk of morbidity and mortality, albeit small. Thus it can be argued that the true "normal" response to pacing, with or without ergonovine, is unknown. Of course, similar objections apply to virtually all studies published to date in which patients with arteriographically normal coronary arteries served as control subjects. These patients have generally undergone arteriography because of chest pain syndromes and therefore are probably more like our subjects, rather than true "normals." Nevertheless, the coronary circulatory response to pacing and vasoconstrictor stimuli exhibited by patients having their typical chest pain during pacing clearly differed from that exhibited by patients not having pain during the study. In addition, none of 10 patients we prospectively suspected as having a noncardiac origin for their chest pain had chest pain or limitation to coronary blood flow during either the control or ergonovine studies. Thus, we believe the patients not having chest pain are a reasonable control group.

The absence of ST-segment depression during pacing-induced chest pain may reflect either a patchy, diffuse distribution of abnormal small vessels, or a nonhomogenous response to pacing or to vasoconstrictor stimuli. Additionally, if a diffuse distribution of myocardial ischemia exists, it might result in a cancellation of electrical forces, thereby accounting for the lack of ST-segment shifts observed during induced ischemia. Similar reasoning may explain the absence of ST depression during exercise testing in most of these patients, despite limitation by chest pain.

Causes of abnormal vasodilator reserve: Whether the microcirculatory abnormalities demonstrated in these patients is an expression of "small vessel spasm" and represents 1 end of the spectrum of coronary vasospastic phenomenon, or reflects morphologic small-vessel disease as has been reported in diabetes[24,25] and other diseases,[25] is unknown. Opherk et al[26] found that a group of patients with chest pain, abnormal exercise stress testing and normal epicardial coronary arteries had a limited pharmacologic vasodilator reserve after dipyridamole infusion compared with patients with atypical and presumably noncardiac chest pain. Endocardial biopsies performed in a subset of these patients revealed only minor mitochondrial abnormalities, although the small arteries we are concerned with—in the 100 to 300 μm range—cannot be adequately sampled by this technique. Another possible cause for the abnormalities demonstrated in our patients would be an underlying cardiomyopathic process with increase in diastolic filling pressures that would adversely affect myocardial blood flow.[27] However, the resting ventricular function by contrast ventriculography and LVEDP in most patients in this study were normal.

A recent report by Opherk et al[28] demonstrated limited pharmacologic vasodilator reserve after dipyridamole infusion in patients with longstanding hypertension and left ventricular hypertrophy on electrocardiography. Thirteen patients in our study were hypertensive by history (none had left ventricular hypertrophy on electrocardiography). Of these, 8 had chest pain during the control study and an additional 2 had chest pain during the ergonovine study. In addition to these 10, 3 patients without a history of hypertension had a mean arterial blood pressure $\geq$110 mm Hg in the catheterization laboratory: each subject had chest pain during the control or ergonovine studies or both. Of these 13 hypertensive patients with pacing-induced chest pain, 10 had an increase in coronary resistance and a decrease in GCV flow after ergonovine administration in a manner identical to the 18 normotensive patients with chest pain after ergonovine. Thus, the majority of patients with hypertension in our study who had chest pain appeared to have dynamic abnormalities of the coronary microcirculation.

The prevalence of myocardial ischemia as the cause of the chest pain in subjects with "normal" coronary arteries is unknown. Based on our experience, however, we suspect it is not uncommon in patients who have the type of pain patterns an experienced clinician believes include many of the characteristics of myocarcdial ischemia.

The question naturally arises as to how patients with abnormal vasodilator reserve can be identified, since electrocardiographic exercise studies are usually negative and the coronary tone study we performed for investigational purposes cannot be considered a practical diagnostic approach for routine clinical use. Radionuclide testing may offer a noninvasive solution to this dilemma, as most patients considered to have small-vessel abnormalities in this study also had abnormal ejection fraction responses or wall motion abnormalities during exercise.[20]

Therapeutic interventions must usually be considered, as these patients often have incapacitating chest pain. Nitrates seem to be effective in controlling symptoms in some patients, but most of the patients referred to the National Institutes of Health have been refractory to usual antianginal medications. Recent studies we have performed suggest that calcium-channel blockers control chest pain very effectively in patients with this syndrome, probably as a result of their potent arteriolar vasodilating properties.[29]

The prognosis of patients with chest pain and normal coronary arteries has been considered to be benign.[30,31] However, patients often continue to have significant and debilitating chest pain despite repeated reassurance.[32] Moreover, in the subgroup of such patients with documented abnormal coronary tone, we have found that 17% had regional wall abnormalities at rest, often associated with reduced global ejection fraction. These latter findings suggest that myocardial necrosis can occur in these subjects in the absence of abnormalities of the epicardial coronary arteries. Hence, the ultimate prognosis of those patients who have myocardial ischemia as the basis for their chest pain may not be so

benign; however, long-term follow-up studies will be required to define the natural history of this interesting condition.

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Dynamic Coronary Obstruction as a Cause of Angina Pectoris: Implications Regarding Therapy

STEPHEN E. EPSTEIN, MD, RICHARD O. CANNON III, MD, RITA M. WATSON, MD, MARTIN B. LEON, MD, ROBERT O. BONOW, MD, and DOUGLAS R. ROSING, MD

The strong link demonstrated at autopsy between coronary atherosclerosis and angina pectoris led to the important concept that a fixed obstruction of 1 or more coronary arteries was the pathophysiologic cause of angina: myocardial ischemia and angina occurred when myocardial oxygen demand outstripped the capacity of the diseased coronary artery to deliver oxygen. Therapeutic strategies were based on attempts to lower myocardial oxygen needs induced by physical and emotional stress. However, the finding that dynamic increases in coronary vascular resistance can also either precipitate ischemia or reduce the threshold of myocardial oxygen consumption ($M\dot{V}O_2$) at which it occurs has profoundly altered our understanding of the pathophysiologic features of angina and, therefore, its treatment. Dynamic coronary obstruction can occur at the large-vessel level, causing Prinzmetal's or variant angina. It is also possible that in some patients a continuum of large-vessel coronary vasoconstrictor tone exists, causing the common clinical situation manifested by angina with variable thresholds of onset. Recent studies have demonstrated that increases in the resistance offered to flow by small coronary arteries too small to be imaged by angiography can also decrease anginal threshold. The fact that ischemia can be precipitated by dynamic increases in large- or small-vessel coronary resistance has important implications for the therapy of angina pectoris. In those persons who mostly have a dynamic component contributing to their coronary obstruction, primary intervention with vasodilator therapy, including nitrates and calcium-channel blocking agents, are probably most effective therapeutically. In those persons with fixed obstruction and little evidence of a dynamic component, the traditional therapeutic approach designed to reduce myocardial oxygen consumption would be most efficacious. This would include the use of nitrates and β blockers. On the other hand, those persons who have a combination of fixed and dynamic obstruction might benefit either from interventions designed either to lower $M\dot{V}O_2$ or to relieve obstruction; some patients might require both approaches for optimal symptomatic control. The recognition that dynamic influences can profoundly exacerbate the degree of coronary obstruction at either the large- or small-vessel level should influence medical approaches to the alleviation of ischemic pain and result in more effective treatment of anginal syndromes.

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Over 40 years ago, a strong link was demonstrated between the coronary atherosclerosis observed at autopsy and the clinical syndrome of angina pectoris.[1] Since that time, the belief has evolved that angina is due to fixed obstructions that limit the capacity of the coronary artery to augment flow in response to increased metabolic demands: angina occurs when a threshold—beyond which further increments in oxygen delivery can no longer be achieved—is reached. In the past decade, however, 2 important developments have effectively refuted the concept that fixed stenosis can entirely account for the diverse clinical syndromes characterized by angina. The first major challenge was the demonstration that large-vessel coronary spasm is the major cause of Prinzmetal's or variant angina.[2–5] This seminal observation totally altered our understanding of the pathophysiologic make-up of angina; it introduced the concept that *dynamic* increases in large-vessel coronary obstruction might occur that could precipitate ischemic symptoms. The second major challenge to the primacy of fixed large-vessel obstruction as the sole cause of angina in patients with ischemic heart disease was the very recent demonstration that abnormal vasocon-

From the Cardiology Branch, the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland.

Address for reprints: Stephen E. Epstein, MD, Cardiology Branch, National Heart, Lung, and Blood Institute, Building 10, Room 7B-15, National Institutes of Health, Bethesda, Maryland 20205.

strictor influences affecting the *small* coronary arteries can precipitate both rest and exertional angina, even in the absence of large-vessel obstructive disease.[6]

The recognition that dynamic increases in either large- or small-vessel coronary resistance can precipitate or exacerbate angina has profoundly altered our approach to the treatment of angina pectoris. In this article we review the concept of dynamic coronary obstruction and outline its impact on our therapeutic approach to the patient with angina.

Normal Mechanisms Controlling Coronary Flow

The normal coronary system consists of large epicardial vessels, which normally function largely as passive conduits and offer little intrinsic resistance to flow (R_1, Fig. 1). The intramyocardial arterioles, on the other hand, alter their intrinsic tone in response to the demands of the myocardium for oxygen. Because of their small diameter and well-developed media, they have the capacity to alter resistance to flow profoundly (R_2, Fig. 1). Because flow is inversely related to resistance (and directly related to driving pressure), this analysis indicates that myocardial flow is inversely related to R_2. Through the autoregulatory system provided by the arterioles, myocardial oxygen delivery and myocardial oxygen consumption ($M\dot{V}O_2$) are tightly coupled: when $M\dot{V}O_2$ increases the resistance vessels dilate and thereby permit myocardial flow to increase in proportion to the increased oxygen demands.

When a large epicardial vessel is narrowed by an atherosclerotic lesion, its conductance function is compromised and it now offers considerable resistance to flow. If no other alteration occurs, the increased resistance leads to a decrease in flow and thereby causes ischemia. However, ischemia-induced metabolic derangements activate autoregulatory mechanisms, resulting in arteriolar dilatation and decrease in R_2. Because R_1 and R_2 (Fig. 1) are in series, total coronary vascular resistance returns toward normal. Further increases in large vessel obstruction cause progressive arteriolar dilatation, and resting flow will remain normal until the vasodilator reserve of the arterioles is exceeded.

Although this compensatory mechanism may prevent the appearance of ischemia under resting conditions, it is not adequate to prevent ischemia when large increments in flow are required, as with exercise. During exercise, once the vasodilator reserve of the arterioles is exhausted, flow can no longer increase as a result of further decreases in resistance. When this maximal flow threshold is exceeded, myocardial ischemia and angina appear.

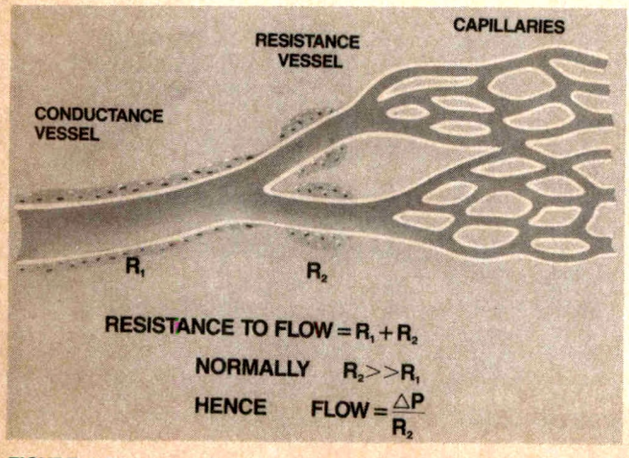

FIGURE 1. Diagrammatic representation of coronary artery. R_1 signifies the resistance to flow posed by the large conductance vessel and R_2 represents resistance to flow posed by the small resistance vessels, or arterioles. ΔP = driving pressure across the coronary bed. Reproduced with permission from *Am J Cardiol.*[11]

Dynamic Coronary Obstruction

Although the concept of fixed obstruction provides a ready explanation for the onset of angina with exercise when $M\dot{V}O_2$ increases considerably, it cannot explain the onset of angina occurring at rest without obvious increase in $M\dot{V}O_2$. This implies that resting flow diminishes and, therefore, that resistance to flow must increase. The concept of fixed obstruction also does not explain why anginal threshold should vary markedly during different times of the day, different times of the week or different seasons of the year, as it so frequently does in patients with angina. For example, patients often report that in the morning relatively mild activities precipitate angina, but as the day progresses the same activities can be undertaken without pain.

Large-vessel spasm: The pioneering studies of Maseri,[7] Oliva[8] and their co-workers demonstrated that large-vessel spasm can decrease flow in a "normal" coronary artery or one narrowed by atherosclerotic plaque, and thereby precipitate transient episodes of angina at rest.[2–4] Additional studies have suggested that spasm-induced decrease in myocardial blood flow is not only responsible for variant angina, but can lead to unstable angina, myocardial infarction and sudden death.[3,4,8] These observations have been of critical importance in understanding the mechanisms contributing to the precipitation of angina. However, although the concept of spasm could be invoked to account for the previously unexplained appearance of pain at rest, the cause of the often marked variations in exertional anginal threshold remained unexplained.

The demonstration that angina occurring during exercise, particularly if associated with ST-segment elevation, was on occasion associated with exercise-induced narrowing of large coronary arteries,[9,10] offered one explanation for the marked variations in exercise capacity in many patients with angina.

It was subsequently suggested that variable threshold angina might also be caused by more subtle vasoconstrictor influences playing on the large coronary arteries that, although not causing total or near total coronary obstruction at rest, was severe enough to interfere with the normal augmentation of flow that occurs with exercise.[11] Thus, the concept of coronary spasm was broadened. At one end of the spectrum is spasm so severe that it causes total or near-total coronary obstruction and results in pain at rest. At an intermediate point of the spectrum, we might find mild large-vessel coronary vasoconstriction leading to a diminished threshold of exercise-induced angina. At the other end

TABLE I Strategy for Treating Angina Pectoris Dependent on Presence or Absence of Dynamic Coronary Constriction

	↑MBF		↓$M\dot{V}O_2$		
	Nitroglycerin	Calcium Antagonists	β Blockers	Nitroglycerin	Calcium Antagonists
Dynamic coronary obstruction	+	+	−	−	−
Fixed obstruction	−	−	+	+	+
Fixed and dynamic obstruction	+	+	+	+	+

↑MBF = increased myocardial blood flow; ↓$M\dot{V}O_2$ = decreased myocardial oxygen consumption; + = mechanism probably leading to effective therapy; − = mechanism probably leading to ineffective therapy.

of the spectrum, coronary tone might actually diminish, with the resulting vasodilation leading to improved exercise capacity.

How resistance to flow can be profoundly altered by small changes in large-vessel coronary diameter can be appreciated by considering some simplified hydrodynamic principles. For example, Poiseuille's law states: $Q = (\pi r^4/8\mu) \times (\Delta P/L)$ where Q = flow, r = the radius of the vessel, μ = the viscosity of blood, ΔP = the driving pressure across the coronary bed and L = the length of the vessel or obstructing lesion. Because $R = \Delta P/Q$, then $R = 8\mu L/\pi r^4 = 8(0.04) \times 16 \times L/\pi D^4 = 1.63 \times L/D^4$ where R = resistance to flow and D = the diameter of the vessel. Thus, resistance to flow is directly proportional to the length of the lesion or vessel, but most importantly is inversely proportional to the fourth power of the vessel diameter.

These concepts are graphically illustrated in Figure 2. The epicardial coronary artery, the diameter of which averages about 3 mm, offers little resistance to flow under normal situations; the major resistance to flow occurs in the small arterioles or resistance vessels. However, relatively small dynamic changes in vascular tone involving the large epicardial coronary vessels might have a profound impact on coronary resistance (and hence, flow) if either a preexisting lesion narrowed the vessel even to a "subcritical" degree, or if the increased tone, producing only a moderate decrease in vessel diameter, involved the entire length of the epicardial vessel (because resistance is also directly proportional to its length).

Changes in vasoconstrictor influences playing upon the large epicardial coronary vessels undoubtedly account on occasion for the varying thresholds of exertional angina seen in many patients. However, we have noticed that patients referred to us with variable threshold angina, especially those who had no ST-segment shifts in their electrocardiogram (ECG) during episodes of pain, rarely had large-vessel coronary spasm in response to such vasoconstrictor maneuvers as ergonovine or cold pressor testing.[6] This contrasted with the high frequency of spasm demonstrated in patients with pain at rest who had concurrent shifts in ST-segments of the ECG.[12]

Small coronary artery vasoconstriction and decreased vasodilator reserve: Our observation that standard ergonovine testing usually failed to precipitate coronary artery spasm in patients with variable threshold angina prompted us to measure regional coronary blood flow and resistance in these patients to determine whether their pain might be due to constriction of coronary vessels too small to be imaged by angiography.[6] Although in this study most patients had a component of pain at rest, patients with classic Prinzmetal's angina were excluded by requiring that when ECGs were obtained during episodes of pain no ST-segment shifts were manifested. Patients with significant large-vessel disease were specifically excluded to avoid the inaccuracies inherent in measuring small changes in the caliber of stenotic vessels which, despite the small magnitude of change, could lead to major alterations in coronary vascular resistance (Fig. 2). Great cardiac vein flow was measured by a thermodilution catheter introduced into the coronary sinus and advanced to the great cardiac vein. This vessel drains approximately 90% of the blood flowing through the left anterior descending coronary artery. The protocol involved increasing $M\dot{V}O_2$ by pacing the heart up to rates of 130 to 150 beats/min under control conditions, during cold pressor testing (for which the patient's hand was immersed to the wrist in ice water during the course of the pacing) and during ergonovine infusion (0.15 mg

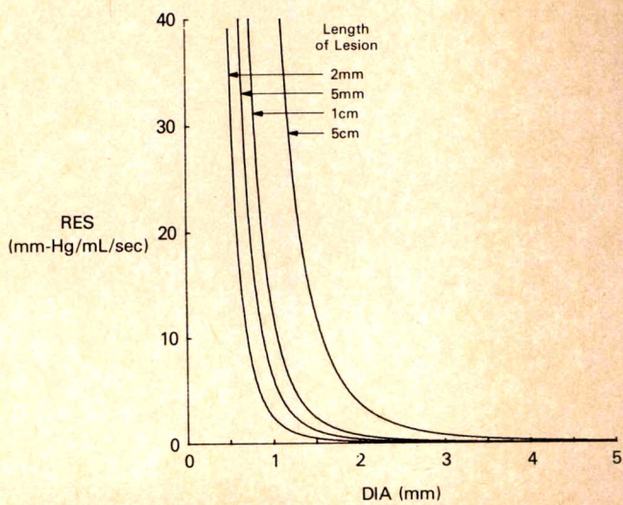

FIGURE 2. Relation between coronary arterial diameter (DIA) and resistance (RES) to flow. Obstructive lesions of different lengths are described by 4 different curves; as length of lesion increases, resistance to flow increases at any given vessel diameter. However, because resistance is inversely proportional to the fourth power of vessel diameter, vessel diameter is the preponderant influence on resistance to flow. Reproduced with permission from *Am J Cardiol.*[11]

administered intravenously).

When the coronary flow and resistance responses were analyzed, persons without chest pain during pacing had large decreases in coronary resistance and increases in great cardiac vein flow. In contrast, these responses were markedly attenuated in those patients in whom pain developed (Fig. 3). Ergonovine infusion resulted in the greatest number of abnormal responses: 2 patients actually had pain at rest during the intervention, which was associated with marked diminutions in coronary flow and increases in resistance. Differences in lactate metabolism between the 2 groups were consistent with the conclusion that the chest pain experienced by the patients with small changes in coronary flow and resistance was indeed due to myocardial ischemia. The fact that the diameter of the large coronary arteries was essentially unaltered with pacing and during vasoconstrictor maneuvers is very important. It indicates that the site at which the abnormal vasodilator reserve or actual constriction occurred was in coronary arteries too small to be imaged angiographically.

Hence, these data provide compelling evidence that abnormalities at the level of the small coronary arteries can contribute to precipitation of myocardial ischemia, either by dynamically increasing coronary resistance in response to vasoconstrictor influences profound enough to cause ischemia at rest, or by restricting vasodilator reserve and thus the potential to augment flow, which would predispose to the development of ischemia during interventions or activities that increase myocardial oxygen requirements.

Although the abnormal coronary vasodilator reserve we demonstrated can be ascribed to vasoconstrictor influences modulating the tone of small coronary arteries,[13–20] our results do not allow us to rule out the possibility that the inadequate vasodilator reserve could be due to abnormal myocardial compressive forces. Thus, a primary abnormality in myocardial relaxation leading to a retardation in the rate of early diastolic relaxation, or the presence of an occult cardiomyopathy

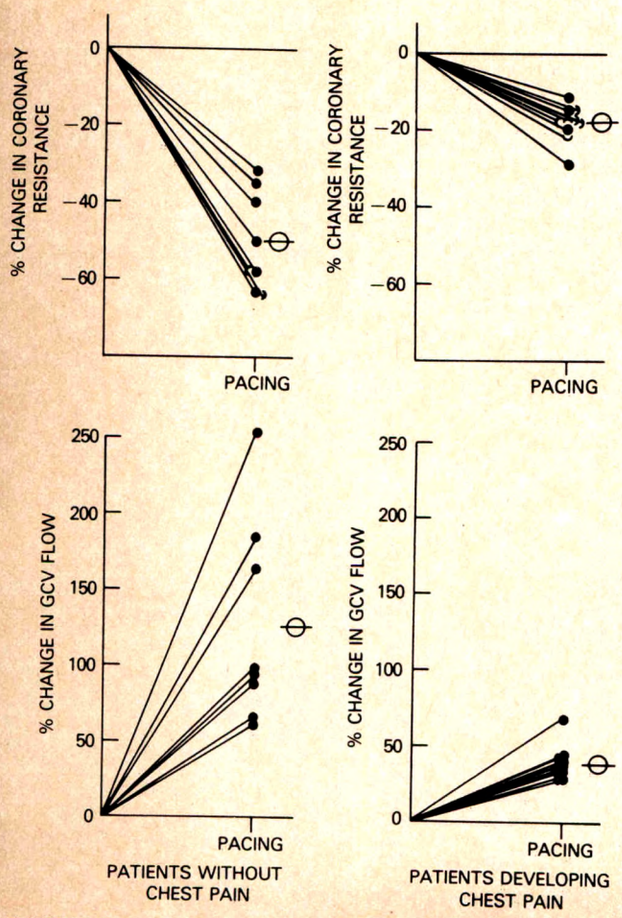

FIGURE 3. Percent change in coronary resistance (calculated from great cardiac vein [GCV] flow and mean arterial pressure) and flow in response to pacing from baseline control heart rate to heart rates of 130 to 150 beats/min. These results were obtained during infusion of ergonovine (0.15 mg intravenously).

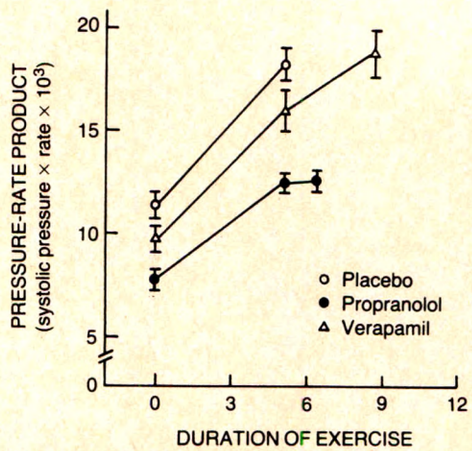

FIGURE 4. Double product (heart rate × systolic pressure) response to exercise of patients under control conditions (**open circles**), during oral verapamil administration (**open triangles**) and during oral propranolol administration (**closed circles**). Exercise intensity was increased by 20 W every 3 minutes. Patients stopped at a symptom-limited endpoint.

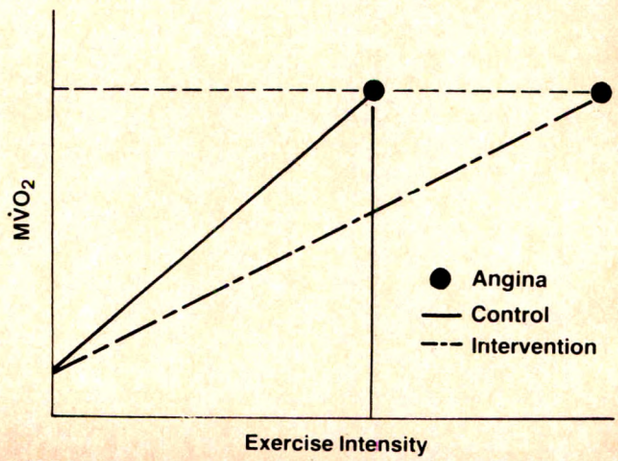

FIGURE 5. Diagrammatic representation of results after intervention that improves exercise capacity by diminishing myocardial oxygen consumption ($M\dot{V}O_2$). With such an intervention, exercise capacity improves but angina occurs at same or lower level of $M\dot{V}O_2$.

leading to increased left ventricular filling pressure, might increase myocardial wall tension during diastole and thereby interfere with coronary flow.[21] It is also possible that the mechanisms responsible for this syndrome are multiple, and that although some persons may have angina as a result of increased vasoconstrictor influences exerted on small coronary arteries, others may have abnormalities of myocardial relaxation or undetected cardiomyopathy.

Effects of Calcium-Channel Blockers on Exercise Responses

Possible effects on myocardial flow: The fact that ischemia can be precipitated by dynamic increases in large or small vessel coronary resistance raises interesting questions regarding the mechanism by which calcium-channel blockers improve exercise capacity in patients with coronary artery disease.[22–33] Although several studies have attempted to elucidate the mechanisms responsible for this salutary effect, definitive data are lacking. However, some insights might be derived by analyzing the results of a randomized double-blind study in which we assessed the effects of verapamil and propranolol on exercise capacity and the circulatory response to exercise.[29] Eleven patients were selected for study who had clinically failed traditional medical therapy, including β blockers and nitrates; several had had unsuccessful coronary bypass surgery. Exercise capacity improved with verapamil when compared with the results attained with either placebo or clinically determined "best dose" of propranolol. In an attempt to determine the possible mechanism of action of verapamil's beneficial effect, we compared the effects of the drugs on the product of systolic pressure and heart rate (double product), an indirect index of myocardial oxygen demand. We found that propranolol, as expected, markedly decreased the double product both at rest and during exercise. The double product also tended to be lower with verapamil. However, although verapamil improved exercise capacity to a significantly greater degree than did propranolol, its double product lowering action was far less (Fig. 4). These findings suggest that although a decrease in $M\dot{V}O_2$ might contribute to the beneficial clinical effects of verapamil, other mechanisms are also probably operative.

This conclusion was reinforced by examining the double product achieved by each of the patients at the time of angina onset. The double product at angina onset is a reflection of the maximal rate at which the obstructed coronary artery is capable of delivering oxygen. If an intervention improves exercise capacity, but the double product at angina is no higher than control levels, it implies that the intervention causes the beneficial effect by decreasing oxygen demands at any level of external stress (Fig. 5). If exercise capacity is improved and double product at angina increases, it implies that the myocardium can attain a higher workload before ischemia occurs, most likely because myocardial flow has increased (Fig. 6).

Figure 7 displays the double product attained at angina onset during placebo and verapamil studies. The double product response to verapamil is markedly heterogeneous; verapamil is associated with the attainment of considerably higher double product levels in 3 patients and in somewhat higher levels in another 3. The remaining patients had either no change or a decrease in the double product at the end of exercise.

These data can be interpretated as demonstrating merely that the double product response to exercise is not reproducible. Alternatively, if only the mean data

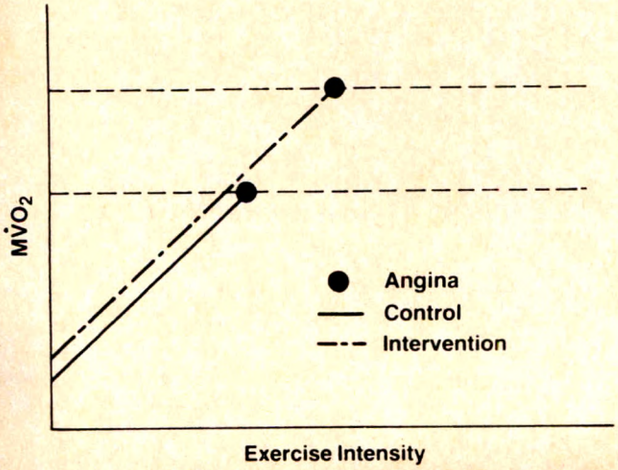

FIGURE 6. Diagrammatic representation of findings after intervention that improves exercise capacity consequent to improvement in myocardial oxygen delivery. Exercise capacity improves and patient is able to exercise to a higher level of myocardial oxygen consumption ($M\dot{V}O_2$) before stopping from angina.

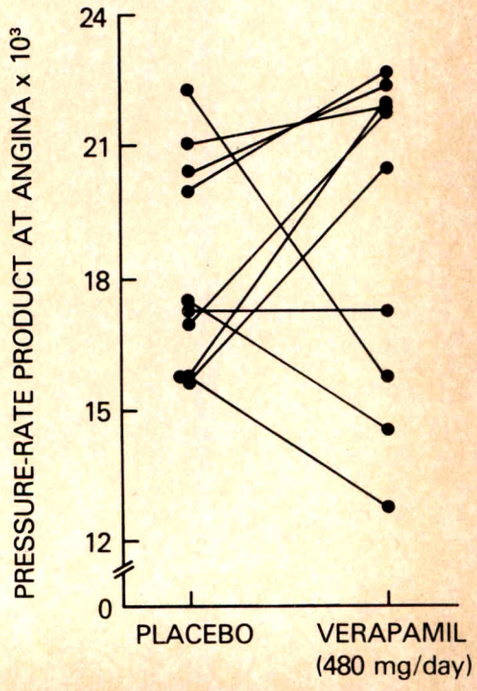

FIGURE 7. Double product at onset of angina under placebo conditions and during long-term administration of oral verapamil. Patients performed exercise on bicycle in upright position and verapamil or placebo was administered in randomized double-blind trial. Reproduced with permission from *Am J Cardiol.*[11]

are examined, it can be concluded that verapamil does not result in the myocardium attaining a higher level of oxygen consumption before the onset of ischemia. A third explanation, however, appears more compatible with the concepts of the pathogenesis of angina we have presented. The mechanisms responsible for the precipitation of angina are heterogeneous and undoubtedly vary considerably from 1 patient to another. Hence, the results depicted in Figure 7 may reflect variability in the mechanisms contributing to the precipitation of angina among the patients. Those patients in whom the double product increased at angina after verapamil administration may have had a dynamic component contributing to flow resistance; the improved exercise capacity produced by verapamil may have been at least partly the result of the drug dilating either the large[34,35] or small[36] coronary arteries, thereby increasing myocardial flow and oxygen delivery.

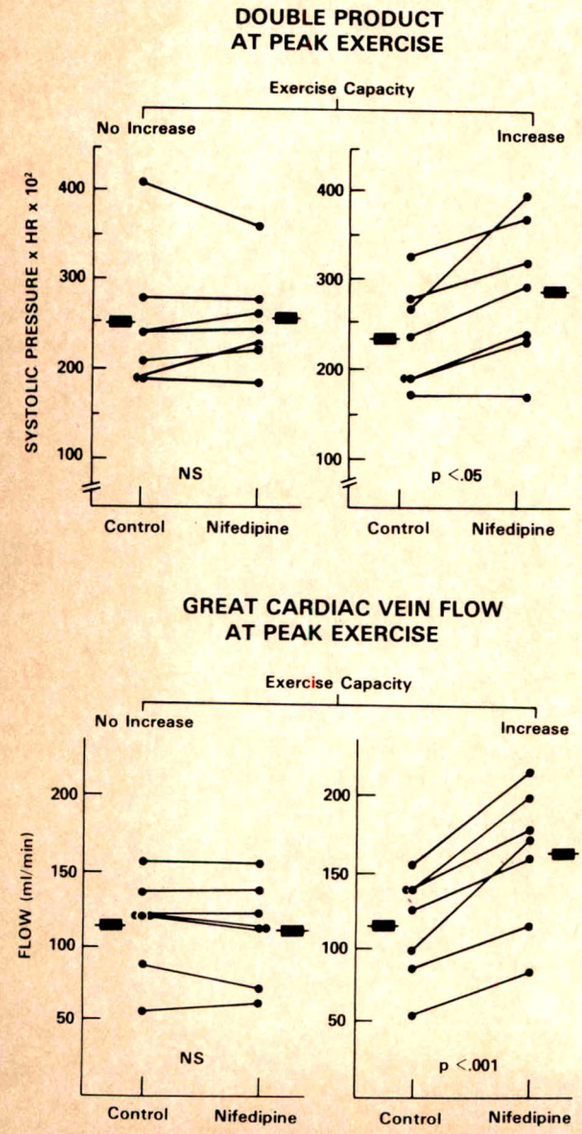

FIGURE 8. Circulatory effects of nifedipine in patients with angina, each of whom had stenosis of left anterior descending coronary artery derived from data by Specchia et al.[37]

This latter explanation is further substantiated by the results of a study examining the effects of nifedipine on both exercise capacity and hemodynamic response to exercise in a group of patients with angina, each of whom had stenosis of the left anterior descending artery.[37] Patients were studied during supine exercise in the catheterization laboratory. In addition to measuring heart rate and arterial pressure, the investigators introduced a flow catheter into the great cardiac vein through the coronary sinus. The great cardiac vein drains flow from the the left anterior descending coronary artery; hence, anterior regional coronary resistance could also be calculated. After nifedipine, exercise capacity showed no change in 7 patients and increased in another 7. The patients with unaltered exercise capacity failed to increase their double products and great cardiac vein flows at peak exercise after nifedipine. In contrast, the patients with improved exercise capacity increased double product and peak flow (Fig. 8). These changes were associated with a decrease in coronary vascular resistance. Zacca et al[38] found similar correlations. When administration of nifedipine improved exercise performance, the improvement was usually associated with an increased double product at peak exercise, as well as an increased left ventricular ejection fraction as determined by radionuclide angiography.[38] Hence, these results are compatible with the hypothesis that 1 of the mechanisms by which calcium-channel blockers improve exercise capacity in patients with angina caused by coronary artery disease is by dilating the coronary arterial system and thereby increasing flow to potentially ischemic regions. Whether the dilatation occurs in the region of the diseased portion of the epicardial vessel, in small coronary arteries or at the arteriolar level is unknown. It is likely that the locus of action varies from patient to patient, depending on the severity of stenosis and whether inadequate vasodilator reserve coexists with large-vessel atherosclerotic disease.

Possible effects on diastolic function: Another possible mechanism contributing to the improvement in symptoms produced by calcium-channel blockers may relate to their ability to improve diastolic function and to reduce inappropriate coronary vasoconstriction. The improvement in left ventricular rapid diastolic filling caused by verapamil[39] could contribute to the enhanced anginal threshold if improved filling reflects an increased rate of isovolumic relaxation, causing in turn an accelerated rate of decrease in myocardial wall tension at the onset of diastole. The resulting decrease in resistance to coronary flow, occurring at a time in the cardiac cycle when flow is usually greatest, would thereby augment myocardial blood flow. It should be pointed out, however, that there are differences in the capacity of the various calcium-channel blocking agents to alter diastolic function. Thus in 1 experimental study in which dose-response curves of verapamil, nifedipine and diltiazem were compared at doses producing equivalent decreases in arterial pressure or resistance, the greatest increase in early diastolic filling rate was

achieved by verapamil and the least by diltiazem.[40] It was also shown that changes in left ventricular filling pressures did not account for these differences.

Treatment Strategy: Concepts of Fixed and Dynamic Coronary Obstruction

Table I outlines the therapeutic approaches implicit in the concepts presented in this report regarding the pathophysiologic mechanisms responsible for the precipitation of angina pectoris. In the patient with variable threshold angina and normal coronary arteries, it can be inferred that coronary flow is impeded by dynamic factors and therefore that interventions designed to decrease coronary resistance and increase flow would appear most appropriate. This can probably best be achieved by the administration of nitrates, calcium-channel blocking agents or a combination of these 2 classes of agents. Administration of β-blocking compounds would probably be largely ineffective, and might even lead to dimunition in exercise performance. Such a paradoxical effect of noncardioselective β blockers was reported in patients with dynamic forms of coronary obstruction.[41–44] It might result from the drugs' capacity to block coronary β_2 (vasodilator)-adrenergic receptors, or from unopposed baroreceptor-mediated coronary vasoconstriction triggered by the blood pressure-lowering effects of the β blockers.

In patients with documented coronary artery disease and with a history of reproducible exertional angina and little or no pain at rest, it can be assumed that a fixed, or relatively fixed, coronary obstructive lesion is the major cause of ischemic symptoms. These persons would probably respond best to nitrates and β-adrenergic blocking drugs. If such patients' symptoms are refractory to this approach, a calcium antagonist can be added because these drugs do have some capacity to decrease $M\dot{V}O_2$.

Patients with a combination of fixed and dynamic obstruction probably constitute a relatively common subgroup of patients. These persons have symptoms of exertion-induced angina, which on superficial questioning may appear to develop at a fairly consistent level of stress. However, a carefully obtained history will usually reveal that the anginal threshold does vary and that episodes of angina at rest are either occasional or frequent. The approach to therapy in this subgroup of patients must be empirical, because it cannot be readily discerned clinically whether the predominant mechanism producing ischemia is related to the fixed or the dynamic component of obstruction. Some patients might respond best to attempts at decreasing myocardial oxygen consumption with the administration of nitrates and β-blocking agents. Others may respond to attempts at relieving the dynamic component of the increased coronary resistance with nitrates and calcium-channel blocking agents. Best results might be achieved in still other patients by combining nitrates, β blockers and calcium antagonists.

In summary, considerable information has accrued over the past few years that has helped to advance our understanding of the mechanisms responsible for precipitating or exacerbating anginal pain. Although atherosclerotic coronary obstructions are critically important in the precipitation of angina pectoris, the recognition that dynamic influences can profoundly alter the degree of coronary resistance at either the large- or small-vessel level will enable the physician to develop more effective medical approches to alleviate ischemic pain.

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Combination Therapy with Calcium-Channel Blockers and Beta Blockers for Chronic Stable Angina Pectoris

MARTIN B. LEON, MD, DOUGLAS R. ROSING, MD, ROBERT O. BONOW, MD, and STEPHEN E. EPSTEIN, MD

Combination therapy using calcium-channel blockers and β blockers in patients with refractory chronic stable angina has gained much popularity, but remains highly controversial because of the potential for serious additive deleterious hemodynamic or electrophysiologic reactions. In studies involving patients with preserved left ventricular function receiving chronic oral β blockers, short-term administration of intravenous verapamil has been shown to cause a further lowering in heart rate and blood pressure while prolonging atrioventricular node conduction; additive cardiodepressant effects were noted, including a tendency toward increased left and right heart filling pressures. Nifedipine, on the other hand, when added acutely to β blockers, causes an increase in heart rate, a decrease in blood pressure and either no change or a slight improvement in most cardiac performance variables. Controlled, double-blind clinical trials have demonstrated that combinations of calcium-channel blockers and β blockers result in augmented symptom benefit compared with either drug class alone. The predominant mechanism responsible for such improvement is increased lowering of myocardial oxygen demand by virtue of additive diminution in heart rate, blood pressure and, consequently, pressure-rate product both at rest and during exercise. Verapamil (and possibly diltiazem) plus β blockers appears to have the greatest therapeutic efficacy but also the highest frequency of harmful adverse cardiac effects, whereas nifedipine plus β blockers is generally safer but also less efficacious. Factors that should be carefully considered by clinicians contemplating combination therapy are the choice of calcium-channel blocker, the dose of calcium-channel blocker and β blocker, the presence of antecedent left ventricular dysfunction or conduction system disease and the possibility of drug interactions.

Concomitant calcium-channel blocker and β-blocker therapy is an important contribution to the pharmacologic management of resistant patients who remain symptomatic during single drug treatment. However, the possibility of additive adverse cardiac effects mandates careful patient selection and close clinical monitoring.

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A remarkable volume of clinical and basic investigation pertaining to calcium-channel blockers has dominated the medical literature over the past several years. As a group, these drugs have been demonstrated to be versatile and important cardioactive agents and have found specific application in all forms of ischemic chest pain syndromes (variant angina, unstable angina and chronic stable angina), systemic hypertension, supraventricular tachyarrhythmias and hypertrophic cardiomyopathy.

From the Cardiology Branch, the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland.

Address for reprints: Martin B. Leon, MD, Senior Investigator, Cardiology Branch, National Institutes of Health, Building 10, Room 7B-15, Bethesda, Maryland 20205.

Verapamil, nifedipine and diltiazem have each been shown to be effective antianginal agents in patients with chronic stable angina. Multiple clinical trials have indicated that these drugs reduce episodes of angina, diminish nitroglycerin consumption, improve exercise performance and lessen ischemic electrocardiographic changes during exercise.[1–10] Previously, β-adrenergic blocking agents, alone and in combination with long-acting nitrate compounds, had been accepted as standard medical therapy in most patients with chronic stable angina. Now, with the broader use of calcium-channel blocking agents for ischemic chest pain, it is useful to consider the potential beneficial interactions between calcium-channel blockers and β blockers, as well as possible adverse drug-related effects.

TABLE I Comparative Effects of Calcium-Channel Blockers on Various Cardiovascular Functions

	Drug		
	Nifedipine	Verapamil	Diltiazem
Heart rate	↑	↓	↓↓
AV nodal conduction	0	↓↓↓	↓↓
Contractility	0	↓↓	↓
Vasodilation	↑↑↑	↑↑	↑
Diastolic filling	↑	↑↑	0

AV = atrioventricular.

Physiologic Considerations

Long before calcium-channel blockers and β blockers were combined in clinical practice, several theoretical concerns regarding combination therapy were raised. Calcium-channel blockers and β blockers have each been shown to reduce heart rate, depress atrioventricular (AV) nodal function, lower blood pressure and reduce myocardial contractility. Moreover, there is evidence to suggest that these groups of drugs induce electrophysiologic and hemodynamic effects by different underlying mechanisms of action.[11] Therefore, it was reasonable to assume that combination therapy might initiate additive and maladaptive changes that could manifest clinically as episodes of bradyarrhythmias, severe hypotension or congestive heart failure.

In contrast to β blockers, calcium-channel blockers represent a pharmacologically diverse and physiologically complex group of drugs. It bears emphasizing that the net hemodynamic effect of a given calcium-channel blocker is the composite of its direct or intrinsic pharmacologic properties and the resultant cardiovascular reflexes evoked (Fig. 1, left). Unfortunately, few clinical studies have examined the differences between calcium-channel blockers in the same patient cohort. Thus an accurate description of comparative cardiovascular effects at equipotent therapeutic dosages becomes problematic. Nevertheless, by extracting data from multiple clinical sources, several generalizations seem appropriate. Verapamil has negative chronotropic and inotropic properties, is a systemic and coronary vasodilator[12] and depresses AV nodal conduction (Table I). Verapamil also improves diastolic filling characteristics measured using both echocardiographic and radionuclide angiographic techniques.[13–15] Nifedipine, on the other hand, behaves predominantly as an arteriolar and possibly arterial vasodilator. In humans with an intact sympathetic nervous system, the hypotension caused by nifedipine elicits a profound reflex sympathetic response that tends to negate any intrinsic effect the drug may have on heart rate, AV nodal conduction and myocardial contractility (Table I). Nifedipine has been shown to improve diastolic filling properties in patients with hypertrophic cardiomyopathy, but to a lesser degree than verapamil.[16,17] Experimental studies in dogs with induced myocardial ischemia[18] have also shown that verapamil improves diastolic filling to a greater extent than nifedipine at doses of the drug that produce equivalent changes in arterial pressure. Diltiazem more closely resembles verapamil than nifedipine, and compared with verapamil seems to result in greater heart rate lowering effects with lesser influences on AV nodal conduction, myocardial contractility and vasodilation (Table I). Although no human data are available at present, preliminary observations derived from canine investigations suggest that diltiazem has little or no effect on diastolic filling behavior.[18]

When β-adrenergic blocking agents are added to calcium-channel blockers, the consequent blunting of reflex β-adrenergic responses constitutes a double-edged sword: it may enhance or unmask intrinsic drug properties that could result in either increased therapeutic efficacy or harmful adverse effects (Fig. 1, right). In patients with normal left ventricular (LV) function and no evidence of conduction system disease, combination therapy usually results in no serious adverse cardiac effects while increasing antianginal potency by virtue of an additive diminution in heart rate, blood pressure and, possibly, contractility, all of which serve to further decrease myocardial oxygen demands. However, the risk-benefit ratio associated with combination therapy may prove disadvantageous in patients with antecedent sinoatrial (SA) or AV nodal conduction system abnormalities who are prone to bradyarrhythmias, or in patients with clinically significant LV dysfunction. Combination β-blocker and calcium-channel blocker therapy may be especially hazardous in patients with congestive heart failure because such persons have little contractile reserve and often have depleted cardiac catecholamine stores, relying mainly on circulating catecholamines to maintain adequate cardiac compensation.

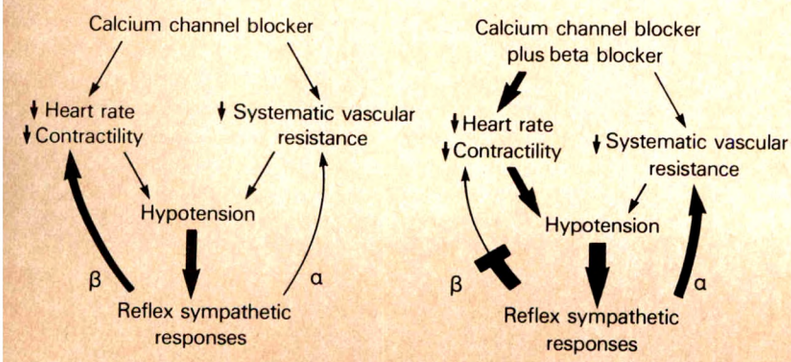

FIGURE 1. Direct and reflex responses induced by calcium-channel blockers alone (**left**) and in combination with β blockers (**right**).

Animal Studies

Early insight into the importance of interactive effects between calcium-channel blockers and β blockers was derived from a variety of canine investigations.[19–21] The short-term administration of intravenous verapamil to dogs resulted in a marked decrease in peripheral resistance, causing reflex sympathetic responses that tended to increase heart rate and cardiac output; direct negative inotropic effects were only partially counteracted by such reflex responses and a decrease in the first derivative of LV pressure (dP/dt) was noted. After pretreatment with propranolol, intravenous verapamil induced similar changes in peripheral resistance but increase in heart rate and cardiac output was partially or totally blunted. Moreover, further increases in LV filling pressures and decreases in dP/dt strongly suggested an additive cardiodepressant effect during combination therapy. Similarly, higher degrees of AV nodal heart block and more frequent episodes of asystole were noted in dogs given intravenous verapamil after pretreatment with propranolol.[22]

In denervated in vitro preparations, nifedipine and verapamil were found to possess comparable intrinsic effects on depressing SA nodal automaticity, AV nodal conduction and myocardial contractility.[23] However, in chronically instrumented conscious dogs,[24] these direct pharmacologic actions were not observed during nifedipine administration, presumably owing to the drugs' potent and preferential vasodilator actions[18] with resulting counterbalancing reflex sympathetic responses. There is a paucity of animal data addressing the concerns of interactive electrophysiologic and hemodynamic effects when either nifedipine or diltiazem are combined with β blockers. In one study,[25] the depressant effects on heart rate, atrial-His (AH) conduction times and AV nodal refractoriness caused by acebutolol were all improved with the concomitant administration of nifedipine, suggesting that secondary reflex responses initiated by nifedipine may protect against deleterious combination drug reactions.

Acute Hemodynamic and Electrophysiologic Studies

In the cardiac catheterization laboratory, Kieval et al[26] studied 20 patients with coronary artery disease and normal LV function (LV ejection fraction ranged from 43 to 79%) receiving relatively small doses of chronic oral propranolol (mean propranolol dose 160 mg/day, mean plasma propranolol level ranged from 66 to 82 ng/ml). Hemodynamic and angiographic variables were measured before and after treatment with intravenous verapamil (0.025, 0.05 or 0.10 mg/kg bolus over 2 min followed by 0.005 mg/kg infusion for 60 min) and the mean plasma verapamil concentration for the entire group at the time of hemodynamic measurements was 168 ng/ml. Intravenous verapamil produced a significant decrease in mean arterial pressure and systemic vascular resistance. Despite the hypotensive effect of verapamil, there was no change in heart rate and no associated improvement in cardiac performance variables (including cardiac index, LV dP/dt and LV ejection fraction). There was no clinical evidence of congestive heart failure as left and right ventricular filling pressures were unchanged. The lack of improvement in cardiac performance in the setting of afterload reduction implies, however, that verapamil caused a mild direct negative inotropic effect. Other investigators have also demonstrated that cardiac output, stroke volume and ejection fraction are unchanged when intravenous verapamil is given *alone* despite similar reductions in systemic vascular resistance.[27,28] Thus, it appears likely that the small implied negative inotropic effects observed by Kieval et al[26] during the short-term administration of intravenous verapamil in patients with preserved LV function receiving small doses of β blockers are not the result of combination drug therapy, but rather are due to verapamil alone.

At the other end of the spectrum, Packer et al[29] evaluated the hemodynamic changes measured during right heart catheterization resulting from the addition of oral verapamil to a group of 15 patients with severe angina at rest and reasonably preserved LV function who were receiving large-dose oral β-blocker therapy (13 patients receiving a mean propranolol dose of 502 mg/day, mean plasma propranolol level 474 ng/ml; 2 patients taking metoprolol 400 mg/day). After the first 120-mg oral dose of verapamil, at which time the average plasma verapamil level was 205 ± 40 ng/ml, there were significant decreases in cardiac index and heart rate associated with increases in both pulmonary capillary wedge pressure and mean right atrial pressure. To determine whether these changes in cardiac performance were due to verapamil alone or to the combination of verapamil and β blocker, β-blocker therapy was withdrawn and the same patient cohort was rechallenged with oral verapamil. Within 24 to 38 hours of β-blocker withdrawal, verapamil produced no significant decreases in cardiac index or heart rate and little change in pulmonary capillary wedge pressure or mean right atrial pressure. These results clearly indicate that the combination of oral verapamil and large-dose β-blocker therapy results in measurable deleterious changes in cardiac function even in patients without severe LV dysfunction (LV ejection fraction ranged from 35 to 78%). Nevertheless, additive drug-related adverse effects were minor; electrophysiologic abnormalities included transient junctional bradycardia in a single patient and hemodynamic disturbances included marked decreases in blood pressure that were unassociated with any symptoms in 2 other patients. Importantly, no instances of clinically overt congestive heart failure were observed.

As with animal investigations, there have been few studies with nifedipine and none with diltiazem examining the short-term additive hemodynamic or electrophysiologic effects in patients receiving long-term β-blocker therapy. Joshi et al[30] studied the effects of adding 10 mg of sublingual nifedipine at the time of cardiac catheterization in 12 patients (8 with coronary artery disease and 4 with no cardiac abnormalities) who were treated with atenolol, 100 mg every 6 hours for 48

hours. Hemodynamic measurements were made during right atrial pacing to a heart rate of 100 beats/min. The addition of nifedipine resulted in marked decreases in mean arterial pressure and systemic vascular resistance. As with verapamil, the expected improvement in cardiac performance usually associated with afterload reduction was not present; although cardiac index did increase, there were no changes in LV ejection fraction or LV end-diastolic pressure, and there was a significant decrease in peak LV dP/dt. Thus, in this small series of patients with normal myocardial function (average LV ejection fraction 61 ± 2%) the combination of small-dose nifedipine and large-dose β blocker caused minor cardiodepressant changes that were similar in direction but lesser in magnitude than those observed with verapamil.

Using a study design combining right heart catheterization and electrocardiographic (ECG)-gated radionuclide angiograms at rest and during exercise, Pfisterer et al[31] studied the short-term hemodynamic effects of combination calcium-channel blocker and β-blocker therapy in 21 patients with angiographically proven coronary artery disease and normal LV function (mean LV ejection fraction 61%). In patients given nifedipine after acebutolol, decreases in ejection fraction, cardiac index and heart rate observed during acebutolol therapy alone were partially normalized with the addition of nifedipine, probably as a consequence of the marked decrease in systemic vascular resistance and the resulting reflex increase in sympathetic stimulation.

The *comparative* effects of verapamil and nifedipine were examined by Winniford et al[32] in 26 consecutive patients with chronic stable angina receiving oral propranolol therapy (mean propranolol dose 234 mg/day) in a short-term study combining hemodynamic evaluation, radionuclide angiography and electrophysiologic testing. In the cardiac catheterization laboratory, measurements were obtained before and after treatment with either intravenous saline solution (n = 6), 0.15 mg/kg of intravenous verapamil (n = 10) or 10 mg of sublingual nifedipine (n = 10). As in previous investigations, intravenous verapamil resulted in decreased heart rate, mean arterial pressure and systemic vascular resistance; cardiac performance variables, instead of improving with afterload reduction, either did not change or showed signs of depressed myocardial contractility. In contrast, nifedipine caused an increase in heart rate, similar decreases in systemic vascular resistance and increases in both cardiac index and ejection fraction. Predictably, verapamil caused prolongation in AH conduction times in all patients without affecting distal conduction, whereas nifedipine had no measurable influence on either AH or HV conduction intervals. Neither verapamil nor nifedipine induced significant changes in resting coronary blood flow as determined using thermodilution coronary sinus catheters.

These hemodynamic and electrophysiologic studies (Table II) show that the short-term administration of either verapamil or nifedipine to patients receiving long-term oral β-blocker therapy further decreases blood pressure and peripheral resistance. Verapamil causes further decreases in heart rate and AV nodal conduction, and appears to depress cardiac function as measured by decreases in cardiac index and LV dP/dt, especially when patients are receiving large doses of β blocker. None of these patients, however, had clinical evidence of LV failure. When nifedipine is added on a short-term basis to small or usual doses of β blockers, there is often an increase in heart rate and either no change or a slight improvement in most indexes of cardiac function. However, when added to large-dose β-blocker therapy, nifedipine may also cause mild depression of myocardial contractility.

There are, however, several critically important limitations to these studies. The likelihood of interactive drug-related adverse effects is certainly dose related (for both β blockers and calcium-channel blockers), is undoubtedly influenced by route and duration of drug administration and is critically dependent on presence or absence of antecedent LV dysfunction and conduction system disease. In the studies summarized in Table II, each patient received a single dose of either β blocker, calcium-channel blocker or both. Whereas patients were usually taking the β blocker on a long-term basis, the

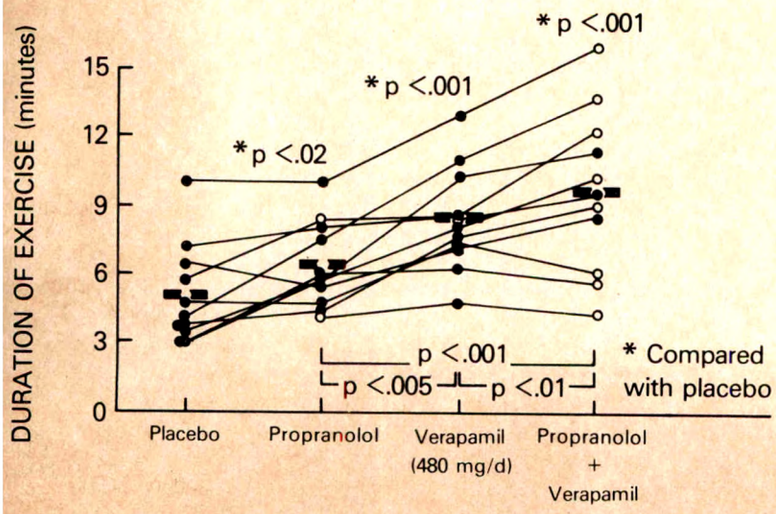

FIGURE 2. Duration of exercise in patients taking verapamil (480 mg/day), propranolol ("best dose") and propranolol ("best dose") plus verapamil (407 ± 25 mg/day). **Broken bars** denote mean exercise time, **closed circles** represent exercise terminated by angina and **open circles** represent exercise terminated by fatigue or shortness of breath.

TABLE II Percent Changes in Hemodynamic and Electrophysiologic Parameters After the Acute Addition of Calcium-Channel Blocker to β Blocker in Patients with Chronic Stable Angina

Investigators	Patients (n)	HR	MAP	SVR	CI	LVEDP	PCWP	LVEF	LV dP/dt	ESVI/ EDVI	AH/HV	CSBF
Verapamil												
Kieval et al[26]	20	−3	−22	−24	0	−14	−9	+2	−7	−3/−2	. . .	. . .
Packer et al[29]	15	−10	−16	−5	−16	. . .	+24	. . .	. . .	. . .	. . .	. . .
Winniford et al[32]	10	−5	−11	−9	−2	. . .	+30	+2	−15	−2/+3	+19/−2	+7
Nifedipine												
Joshi et al[30]	12	Paced	−10	−20	+12	+4	. . .	+5	−9	. . .	. . .	. . .
Pfisterer et al[31]	7	+7	−4	−18	+17	. . .	+6	+4	. . .	. . .	. . .	. . .
Winniford et al[32]	10	+9	−6	−20	+16	. . .	0	+10	+2	−7/+2	+2/0	+15

AH/HV = atrial-His and His-ventricular conduction times, CI = cardiac index; CSBF = coronary sinus blood flow; ESVI/EDVI = end-systolic and end-diastolic volume index; HR = heart rate; LV dP/dt = peak positive left ventricular dP/dt; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

calcium antagonist was administered over the short term. Moreover, and most importantly, all patients had well-preserved LV function. Finally, whereas mean hemodynamic effects of a drug can be assessed in small numbers of patients, such studies cannot take into account the possibility that occasional patients may have aberrant responses. Thus, it is impossible to extrapolate the results of these studies to a more heterogeneous patient population receiving multidrug long-term oral therapy.

It bears emphasizing that additive depression in cardiac performance variables measured during combination verapamil and β-blocker therapy has only rarely been causally associated with episodes of clinical congestive heart failure in patients with preserved LV function.[33] However, in patients with evidence of congestive heart failure, intravenous verapamil *alone* has been shown to induce adverse hemodynamic effects.[34] Moreover, many case reports[35–39] suggest that combinations of either intravenous or oral verapamil and β blockers may cause further clinical deterioration in patients with preexisting hypotension or significant myocardial dysfunction. Similarly, although nifedipine has only rarely been implicated as the sole causative agent leading to hemodynamic or electrophysiologic disturbances in patients with normal LV function,[40] there are preliminary data indicating that nifedipine *alone* may also have clinically important direct negative inotropic effects in patients with congestive heart failure.[41,42] There are also a growing number of reported cases demonstrating that combination therapy with nifedipine and β blockers may result either in severe hypotension or in clinical episodes of congestive heart failure.[43–46] Presumably, attenuation of baroreceptor-mediated compensatory reflexes that normally stimulate cardiac β receptors can unmask intrinsic negative inotropic properties of the drug and precipitate clinical events that are only rarely seen when nifedipine is given alone. Diltiazem, the newest and least extensively studied of the calcium-channel blockers, has only recently achieved widespread clinical use in the United States. Nonetheless, there have already been cases reported of atrioventricular dissociation or sinus nodal arrest or both associated with diltiazem therapy, given alone or in combination with β blockers.[47] Thus, until more clinical experience accrues in patients with depressed LV function and conduction system disease, it is wise to caution against the use of combination therapy with β blockers and *any* calcium-channel blockers in patients who are prone to developing congestive heart failure.

Controlled Clinical Trials

Verapamil: Several clinical trials examined the effects of verapamil plus propranolol in patients with coronary artery disease. We studied 11 patients with severe chronic stable angina and relatively preserved LV function (resting ejection fraction ≥30%) to evaluate the therapeutic efficacy and mechanisms of action of verapamil when administered alone and in combination with β blockers.[4] All patients remained symptomatic after treatment with oral propranolol (mean propranolol dose 225 mg/day, range 160 to 320) and were hospitalized for inpatient evaluation. Patients were given either propranolol (individualized optimal dose established preadmission), placebo or verapamil (320 mg/day followed by 480 mg/day) in single-blind, randomized, triple-crossover fashion. Each drug treatment period was for 48 hours followed by down-titration for 24 hours and 24 hours without medications before advancing to the next drug. After single-drug therapy was completed, all patients were treated with combinations of propranolol and increasing dosages of verapamil (titrated to adverse effect tolerance). Assessment of plasma drug concentrations during active drug administration indicated that steady-state plasma drug levels were achieved for both propranolol (mean plasma level 203 ± 33 ng/ml) and verapamil (mean plasma level with 480 mg/day therapy, 209 ± 29 ng/ml) at the time of exercise testing.

Compared with placebo, which resulted in a mean exercise time of 5.1 min, verapamil (480 mg/day) improved mean exercise duration to 8.5 min ($p < 0.001$) and was more effective than propranolol, which increased mean exercise duration to 6.4 min ($p < 0.005$) (Fig. 2). The combination of verapamil (mean dose 407 mg/day, range 320 to 480) and propranolol (mean dose 255 mg/day) further increased mean exercise performance to 9.8 min, which was significantly better than the results achieved with either propranolol ($p < 0.001$) or large-dose verapamil ($p < 0.01$) (Fig. 2). During exercise, whereas only 2 patients were pain-free with propranolol and 1 was pain-free with verapamil, 9 of 11

patients (82%) had no angina during exercise with the combination of verapamil plus propranolol.

Although 2 patients had transient AV nodal Wenckebach with verapamil alone (1 excluded from study protocol), during combination therapy, no patient had electrocardiographic evidence of new or worsening conduction system abnormalities, as indicated by further PR-interval prolongation, AV nodal heart block or other clinically significant bradyarrhythmias. Moreover, resting LV ejection fraction determined using radionuclide angiography decreased from 48 ± 3% (range 32 to 69) during placebo to 46 ± 3% with propranolol (difference is not significant) and to 44 ± 4% with verapamil ($p < 0.02$ compared with placebo). The addition of verapamil to propranolol did not result in significant additive cardiodepressant effects (ejection fraction 43 ± 4%). LV ejection fraction at rest decreased ≥5% (compared with placebo) in 5 of 11 patients receiving verapamil and in 7 of 11 patients receiving combination verapamil and propranolol therapy. Three patients did describe adverse symptomatic reactions during combination therapy. Two patients noticed postural dizziness associated with orthostatic hypotension (limiting the dose of verapamil) and 2 patients (1 of whom also had dizziness) described exertional dyspnea, 1 with the lowest pretreatment ejection fraction (32%) and another with the greatest decrease in ejection fraction during verapamil alone (from 46 to 31%). Thus, although there were no episodes of overt clinical congestive heart failure noted during combination therapy, in retrospect it seems clear that complaints of exertional dyspnea were early manifestations of LV decompensation.

Bala Subramanian et al[48] studied the comparative efficacy of verapamil (360 mg/day) versus propranolol (240 mg/day) using treadmill exercise testing in 22 patients with chronic stable angina and no evidence of congestive heart failure in a placebo-controlled, double-blind, crossover study consisting of 4-week drug treatment periods. Fourteen patients who remained symptomatic after single-drug therapy were advanced to single-blind combination drug therapy with verapamil (360 mg/day) and propranolol (120 mg/day) for an additional 4 weeks. The mean exercise time for the patient group while taking placebo was 4.8 min; it increased to 6.8 min with propranolol ($p < 0.001$). During combination drug therapy, 7 patients (50%) were without angina during exercise and mean exercise capacity improved to 10.1 min, which was significantly better than either propranolol ($p < 0.01$) or verapamil ($p < 0.05$) alone. In addition, both ST-segment depression and workload achieved during exercise were improved more by combination verapamil-propranolol therapy than by either therapy alone. No serious adverse cardiac or extracardiac effects were encountered during any phase of the drug trial.

Comparing the clinical efficacy of propranolol alone and a verapamil-propranolol combination, Winniford et al[49] investigated 13 men without a history of congestive heart failure who had angina while receiving propranolol therapy (mean propranolol dose 295 mg/day, range 160 to 480). Treatment with propranolol was continued during the entire study and, after open-label verapamil up-titration to establish drug tolerance, all patients were subsequently given either placebo or verapamil (mean verapamil dose 431 mg/day, range 320 to 480) in a randomized, double-blind, crossover study with 2-week drug treatment periods. During propranolol-verapamil therapy, both angina frequency and glyceryl trinitrate consumption diminished significantly compared with propranolol-placebo. The average exercise duration was 6.8 min with propranolol-placebo compared with 8.2 min with propranolol-verapamil ($p < 0.05$). Adverse effects during combination propranolol-verapamil therapy were common; 2 patients had fatigue and dyspnea and 2 others had severe symptomatic sinus bradycardia and junctional escape rhythm. LV ejection fraction (at rest and during exercise) was unchanged after the addition of verapamil to propranolol and no patient had episodes of second- or third-degree AV nodal heart block or objective evidence of LV failure.

These 3 clinical trials convincingly demonstrate that combination therapy with verapamil and propranolol results in additive antianginal efficacy compared with either drug alone as reflected by a decrease in clinical episodes of angina, prolonged exercise capacity and decreased ischemic electrocardiographic changes during exercise. However, the impressive salutary effects were not without some risks. From these 3 trials, it appears that the most serious adverse effects, including hypotension, exertional dyspnea and symptomatic bradycardias, were seen only in the 2 studies using relatively large doses of verapamil and propranolol.[4,49] However, a recent study indicates otherwise.[50] In a double-blind crossover study comparing radionuclide angiographic parameters during verapamil (360 mg/day), propranolol (160 mg/day) and the combination (verapamil 360 mg/day plus propranolol 160 mg/day), 1 of the 19 patients enrolled had symptomatic bradycardia and 3 others had evidence of heart failure during combination therapy.[50] Thus, interactive adverse effects associated with verapamil-propranolol combinations are occasionally unpredictable. The overall frequency of either hemodynamic or electrophysiologic disturbances in the combined studies just reviewed was 14%.[4,48–50]

Nifedipine

Although nifedipine is more often combined with β blockers in outpatient practice than verapamil, it has been the subject of fewer carefully performed clinical trials. Ekelund et al[51] used a double-blind, placebo-controlled, crossover study to compare exercise hemodynamic responses at the end of 3-week treatment periods using a β blocker (metoprolol, 150 mg/day or alprenolol, 300 to 800 mg/day), nifedipine (30 mg/day) and a combination of β blocker and nifedipine in 21 patients with stable exertional angina and no congestive heart failure.[51] The combination of nifedipine and β blocker resulted in a greater diminution in anginal attack frequency and glyceryl trinitrate consumption than could be achieved with either drug alone; furthermore, these favorable effects were associated with an average 41% improvement in total work during exercise com-

pared with placebo. The vast majority of patients (86%) preferred to continue taking combination nifedipine–β-blocker therapy at the completion of the trial and no serious adverse cardiac effects could be attributed to combination drug therapy. Another double-blind, placebo-controlled study using only clinical variables (angina attack frequency and trinitrate consumption) as therapeutic endpoints demonstrated that nifedipine (30 mg/day) plus propranolol (120 mg/day) was clearly superior to placebo or nifedipine alone (30 mg/day) but only marginally better than propranolol alone (240 mg/day). Again, no significant adverse effects were noted in these 20 patients with chronic stable angina during combination nifedipine–β-blocker therapy.[52]

Dargie et al[53] also explored the additive antianginal effect of nifedipine plus propranolol in 16 patients with effort-induced chronic angina and no history of congestive heart failure.[53] Both small and large doses of nifedipine (30 and 60 mg/day) and propranolol (240 and 480 mg/day) were given alone and in combination for 2-week drug treatment periods in a double-blind, placebo-controlled crossover format. Objective study endpoints included patient diaries (recording episodes of chest pain and nitroglycerin consumption), continuous ambulatory ECG monitoring (assessing episodes of ST-segment depression) and precordial ECG mapping during bicycle ergometer exercise (determining extent and severity of exercise-related ischemia). Although both nifedipine and propranolol alone decreased frequency of angina and nitroglycerin consumption, propranolol appeared to be the more effective single agent. Combination therapy with nifedipine and propranolol resulted in decreases in angina frequency and nitroglycerin intake that were only slightly greater than those brought about by propranolol alone. The number of episodes of ST-segment depression during ambulatory ECG monitoring and the area of ST-segment depression during exercise were significantly diminished during combination therapy compared with single drug therapy using either agent. It was observed that nifedipine, 30 mg/day, was less effective than nifedipine, 60 mg/day, for all variables assessed, whereas there was little difference between propranolol, 240 mg/day, and propranolol, 480 mg/day. Adverse effects were frequently described with nifedipine alone (for instance, 40% of patients reported dizziness on standing, 50% of patients had ankle edema), but no significant new or worsening drug-related adverse effects appeared during combination nifedipine-propranolol therapy.

Regrettably, the data generated thus far involving combination nifedipine–β-blocker therapy in controlled clinical trials leave many questions unanswered. The additive antianginal effects in some studies[52,53] were not significantly different from β blockers alone, and the dose of nifedipine used (generally 30 mg/day) may be in the subtherapeutic range for many patients. Nevertheless, there is sufficient combined evidence derived from these investigations,[51,52] from other short-term oral dosing studies,[54] and from studies of patients with unstable ischemic chest pain syndromes[55] indicating that nifedipine–β-blocker treatment in refractory subjects will result in additive therapeutic benefit. Importantly, unlike verapamil, the combination of nifedipine and β blocker was not associated with significant adverse effects in patients without LV dysfunction.

Diltiazem

At present, published reports exploring the potential benefits of combination diltiazem–β-blocker therapy in patients with chronic stable angina remain scanty. Hung et al[56] enrolled 12 patients in a double-blind, crossover, randomized study. The patients performed symptom-limited, upright bicycle exercise while undergoing radionuclide angiography after 2 weeks treatment with diltiazem (360 mg/day), propranolol (240 mg/day) and a combination of diltiazem (360 mg/day) and propranolol (240 mg/day) and placebo. Compared with placebo, diltiazem, propranolol and the combination of diltiazem and propranolol all improved total exercise duration, time to onset of angina and time to ischemic electrocardiographic changes during exercise; there were no differences in any of the active drug treatment groups. The lack of additive antianginal efficacy with combination therapy may be partially explained by the fact that 6 patients with diltiazem alone and 4 patients with propranolol alone were already without angina during exercise testing. In contrast, a preliminary report[57] using more appropriate patient inclusion criteria examined the exercise responses in 12 patients with chronic stable angina treated with diltiazem (180 mg/day), propranolol (240 mg/day) and the combination in a double-blind, placebo-controlled study. It demonstrated significantly greater antianginal benefit during combination therapy compared with either agent alone.

Although diltiazem as a single agent in dosages <240 mg/day is accompanied by only occasional adverse effects,[58–60] Hung et al[56] described a disturbing frequency of interactive adverse drug effects with diltiazem-propranolol combinations; 3 patients had a resting sinus bradycardia <45 beats/min (1 of whom also had orthostatic dizziness), another patient had severe orthostatic dizziness accompanied by postural hypotension and a fifth patient had short episodes of sinoatrial pauses. Other investigators using similar dosages of diltiazem-propranolol combinations in patients with coronary vasospasm have also described a tendency toward severe sinus bradycardia.[61] Finally, there was no evidence of LV dysfunction or episodes of clinical congestive heart failure during any treatment group in this study,[56] but the number of patients treated was too small to derive any conclusion concerning the possibility of LV dysfunction developing with diltiazem–β-blocker therapy.

Comparative Clinical Efficacy

Attempts to compare relative therapeutic efficacy of different calcium-channel blockers used in combination with β blockers are frought with complex methodologic considerations. Factors that can never be equalized retrospectively include drug dosage (for both calcium-channel blocker and β blocker), duration of therapy, vagaries of study design, such as differences among exercise protocols, and patient selection criteria. Nev-

ertheless, given these considerable limitations and the small number of controlled clinical trials available for analysis, the combination of verapamil and propranolol would appear to be the most beneficial, if the percentage of change in exercise performance is used as the sole criterion for additive therapeutic efficacy (Fig. 3).

An alternative approach to assess relative therapeutic potency among various calcium-channel blockers when combined with β blockers was used by Bassan et al.[62] Ten men with stable angina not fully relieved by optimal doses of propranolol (mean propranolol dose 218 mg/day, range 60 to 360) were given on each of 4 separate days, in addition to chronic propranolol, a single dose of either nifedipine (10 mg), verapamil (120 mg), isosorbide dinitrate (5 to 30 mg) or placebo in double-blind crossover fashion. Symptom-limited bicycle exercise tests were performed hourly for 8 hours and all 3 agents were shown to prolong exercise duration by at least 50% by the first hour ($p < 0.001$) with a gradual diminution in antianginal effect by the eighth hour ($p < 0.01$). Although no group differences in relative therapeutic efficacy could be demonstrated among the agents, in half the patients either the magnitude or duration of beneficial effects favored one or another vasodilator. Caution, however, is advised in the interpretation of such short-term oral dosing studies involving vasodilators. Marked preload and afterload reduction associated with short-term, single-dose treatment is often attenuated during continuous therapy, resulting in diminished antianginal effects. Therefore, attempts to extend these findings to the more realistic clinical setting of long-term oral multidrug therapy may not be justified.

Mechanisms of Action

There are many underlying pathophysiologic mechanisms responsible for the favorable clinical responses seen in patients with coronary artery disease treated with calcium-channel blockers. Like other antianginal agents such as nitrates and β blockers, each of the calcium-channel blockers (to varying degrees) has the effect of reducing several of the hemodynamic determinants of myocardial oxygen demand. Pressure-rate product, which loosely reflects myocardial oxygen consumption, is reduced compared with placebo, at rest and during matching levels of exercise with single drug therapy using verapamil[4–6,63] (Fig. 4), nifedipine[7,8,64] and diltiazem.[10,65] Moreover, at symptom-limited termination of exercise, the pressure-rate product attained is similar to placebo endpoint values (Fig. 4). These findings have been interpreted to imply that the predominant mechanism of action of calcium-channel blockers is restricted to influences on oxygen demand and unrelated to changes in coronary vasomotor tone and myocardial oxygen delivery. Yet, this appears to be an oversimplification of a complex series of interrelated physiologic events. Quantitative coronary angiographic techniques have demonstrated that verapamil is a mild epicardial coronary vasodilator in patients with coronary disease, and also inhibits neurally mediated and ergonovine-induced vasoconstriction.[12] Recently, nifedipine has been shown to increase great cardiac vein blood flow (and peak pressure-rate product at angina) while reducing anterior regional coronary resistance in those patients with stable effort angina manifesting the greatest antianginal effects.[66] Closer examination of individual patient data from reported studies[4] also re-

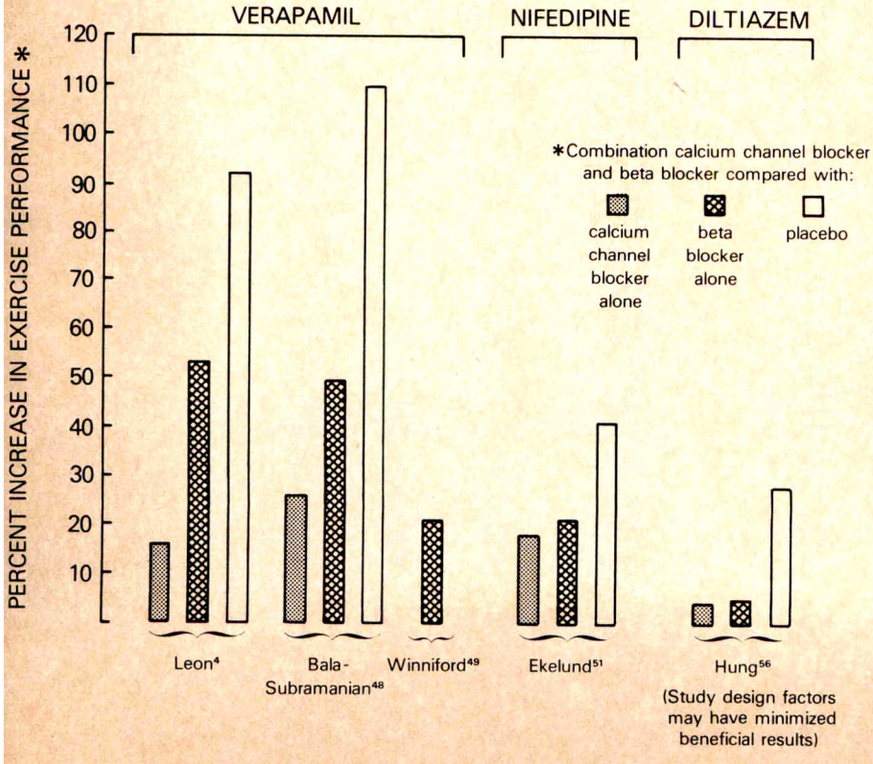

FIGURE 3. Percent increase in exercise performance during combination calcium-channel blocker (verapamil, nifedipine or diltiazem) and β-blocker therapy compared with placebo, calcium-channel blocker alone and β blocker alone.

TABLE III Percent Changes in Hemodynamic Variables at Rest and During Exercise After the Addition of Calcium-Channel Blocker to β-Blocker Therapy

β Blocker plus:	ΔHR (%)		ΔSBP (%)		ΔPRP (%)	
	R	Ex	R	Ex	R	Ex
Verapamil						
Leon et al[4]*	−6	−7	−15	−16	−20	−22
Winniford et al[49]†	−2	−7	−4	−5	−5	−11
Nifedipine						
Ekelund and Oro[51]*	+9	−1	−11	−14	−8	−14
Diltiazem						
Hung et al[56]*	−4	−9	−12	−8	−16	−16

* At placebo endpoint exercise.
† At termination of exercise.
Ex = exercise; HR = heart rate; PRP = pressure-rate product; R = rest; SBP = systolic blood pressure.

veals that some patients have marked increases in peak pressure-rate product achieved during exercise after treatment with verapamil, suggesting a primary increase in myocardial oxygen supply. Finally, if changes in diastolic filling characteristics caused by calcium-channel blockers have therapeutic consequences in patients with coronary artery disease, a contributing mechanism would include an improvement in transmyocardial coronary perfusion.

The assumption that pressure-rate product analysis incorporates all factors influencing myocardial oxygen demand is also an oversimplification. Calcium-channel blockers, by virtue of their negative inotropic effects or change in loading conditions that alter LV geometry, can modify myocardial oxygen demand independent of their effects on heart rate and blood pressure. In addition, animal and human studies suggest that verapamil may cause changes in *regional* systolic function, which are most marked in ischemic myocardium; these effects are different from those observed with β-blocking agents.[50,67] The situation is further complicated by the fact that underlying pathophysiologic mechanisms responsible for angina may differ among patients, and include, to varying degrees, fixed atherosclerosis, superimposed coronary vasospasm and reduced ventricular compliance. It would therefore be difficult to define a specific mode of action of a calcium-channel blocker in an individual patient, as the drugs could exert their salutary effects by decreasing myocardial oxygen demand, increasing myocardial oxygen supply or improving LV compliance.

Although the mechanism of action of a calcium-channel blocker as a single agent in the treatment of chronic stable angina is controversial, there is a clearer explanation for the additional benefits derived from combination therapy with β blockers. Compared with either class of drug alone, the addition of β blockers to calcium-channel blockers results in further decrease in heart rate, blood pressure and, consequently, pressure-rate product both at rest and during exercise, causing a significant additive diminution in myocardial oxygen demand (Table III). Moreover, concomitant calcium-channel blocker and β-blocker therapy initiate offsetting physiologic responses that attenuate the

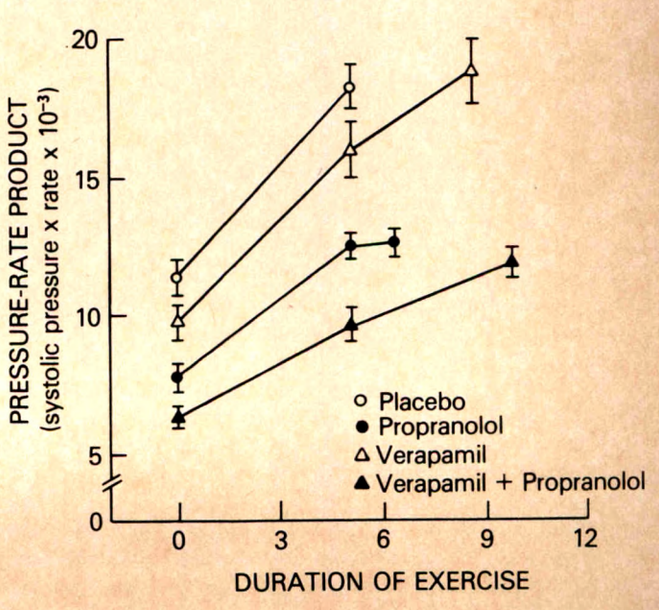

FIGURE 4. Pressure-rate product responses at rest before exercise, at placebo endpoint of exercise and at termination of exercise. Data are expressed as mean ± standard error of the mean with various drug therapies.

potentially negative effects of each individual drug (Table IV). For instance, baroreceptor-mediated reflexes causing sympathetic stimulation of the heart induced by calcium-channel blocker therapy may diminish their effectiveness by blunting their direct negative chronotropic and inotropic influences on myocardial oxygen demand; combination therapy with β blockers would partially negate these reflex responses and improve therapeutic efficacy. Similarly, unopposed α-adrenergic–mediated coronary vasoconstriction in β-blocked patients would be partially or completely reversed during combination therapy with calcium-channel blockers. Thus, combined drug therapy appears beneficial in relieving symptoms of angina, not only because of individual favorable drug actions but also because, when used together, each drug may serve to oppose the unfavorable cardiovascular effects of the other.

Therapeutic Implications

The proper clinical use of combination calcium-channel blocker and β-blocker therapy in patients with chronic stable angina still remains controversial. At the present time, it would be impossible to propose a universal formula that would apply to all patient subsets in all clinical circumstances. Therefore, decisions regarding combination therapy must be made on a case-by-case basis and are dictated by careful attention to each of the following factors.

Choice of calcium-channel blocker: The calcium-channel blockers possess diverse and differing pharmacologic properties. Heart rate-lowering vasodilators, such as verapamil and diltiazem, appear to be the most effective antianginal agents and have the lowest incidence of significant adverse *extracardiac* effects. However, when combined with β blockers, these drugs also have the highest incidence of adverse *cardiac* effects. Verapamil may precipitate or exacerbate congestive heart failure and may cause bradyarrhythmias more often originating from the AV node, whereas diltiazem more frequently causes bradyarrhythmias originating from the SA node. On the other hand, a vasodilator that lacks heart rate-lowering effects, such as nifedipine, appears to be a less effective antianginal agent, alone or in combination with β blockers. Further, in therapeutically important dosages (from 60 to 120 mg/day), nifedipine has the highest incidence of significant adverse *extracardiac* effects. It is important to note that nifedipine added to β blockers is generally viewed as a safe drug combination from the standpoint of adverse *cardiac* effects; rarely is congestive heart failure or bradyarrhythmias a problem, and additive hypotension can usually be reversed with careful dose titration.

Dose of calcium-channel blocker and β blocker: Although increasing doses of calcium-channel blockers tend to favor augmented therapeutic benefit,[4,6,53] during combination therapy with β blockers attempts to use larger doses must be tempered by the potential for serious additive hemodynamic or electrophysiologic consequences. For example, the only study demonstrating a significant decrease in LV ejection fraction with oral verapamil alone used 480 mg/day dosages;[13] in contrast, other studies using similar radionuclide angiographic techniques and lower dosages of verapamil (320 mg/day) found no changes in ejection fraction.[68] Similarly, unusually large doses of β blockers were implicated by Packer et al[29] as the major cause for additive cardiodepressant effects found in their study of combination drug therapy. Given the data thus far available, it seems prudent when contemplating combination therapy to treat with somewhat smaller than normal doses of both calcium-channel blockers (especially verapamil and diltiazem) and β blockers.

High-risk patient subgroups: Patients with clinically apparent LV dysfunction, a propensity for developing bradyarrhythmias (either at the SA or AV nodal level) or hypotension should be considered at high risk to develop complications from combination calcium-channel blocker and β-blocker therapy. Although most studies have carefully excluded patients with moderate or severely depressed LV function, it seems clear from hemodynamic evidence that combination therapy in such patients should favor nifedipine; diltiazem and especially verapamil should be completely avoided or used at small dosages with extreme caution. Verapamil has been shown to depress sinus nodal function in patients with sick sinus syndrome[69] and diltiazem has the greatest negative chronotropic effects among all calcium-channel blockers.[70] Therefore, neither should be used with β blockers in patients with signs of sick sinus syndrome, including severe sinus bradycardia at rest. Verapamil, and to a lesser extent diltiazem, are also relatively contraindicated during combination therapy in patients with evidence of antecedent AV nodal disease (marked PR-interval prolongation or higher degrees of AV nodal heart block). Finally, in patients with borderline hypotension, treatment with potent vasodilators like nifedipine, either alone or particularly in combination with β blockers, may be extremely hazardous and should be approached with caution.

Other drug interactions: In addition to β-adrenergic–blocking agents, other cardioactive medications combined with calcium-channel blockers may result in deleterious interactive effects. Drugs with negative inotropic properties, such as disopyramide, may potentiate the cardiodepressant actions of calcium-channel blockers (especially with β blockers) and are relatively contraindicated. During combination calcium-channel blocker and β-blocker therapy, maintenance of circulatory homeostasis is disproportionately dependent upon reflex α-adrenergic sympathetic responses (Fig. 1, right). Therefore, other potent arteriolar dilators (such as hydralazine, prazosin and captopril) and drugs with central or peripheral α-adrenergic–blocking properties (such as clonidine, methyldopa and possibly quinidine) may also precipitate severe symptomatic hypotension when added to calcium-channel blockers (particularly nifedipine). Finally, intrinsic negative chronotropic and AV nodal depressant effects of verapamil and diltiazem are exaggerated in the presence of both β blockers and digoxin, independent of the changes induced by calcium-channel blockers on digoxin metabolism and clearance.[71]

TABLE IV Factors Influencing Myocardial Oxygen Supply-Demand Relation During Treatment with Calcium-Channel Blockers, β Blockers and the Combination

	Calcium-Channel Blockers				Calcium-Channel Blockers + β Blockers		
	V	N	D	β Blockers	V	N	D
Myocardial oxygen supply							
Coronary vasomotor tone	↓↓	↓↓	↓↓	↑	↓	↓	↓
Diastolic filling	↑↑	↑	0	0	↑↑	↑	0
Myocardial oxygen demand							
Heart rate	↓	↑	↓↓	↓↓	↓↓↓	↓	↓↓↓↓
LV systolic wall tension	↓	↓↓	↓	↓	↓↓	↓↓↓	↓↓
Contractility	↓↓	0	↓	↓	↓↓↓	↓	↓↓

D = diltiazem; LV = left ventricular; N = nifedipine; V = verapamil.

As our experience broadens, several general statements concerning combination calcium-channel blocker and β-blocker therapy may be helpful in guiding the practitioner. First, combination therapy should be reserved for only those patients with chronic stable angina who continue to have severe symptoms despite an adequate trial using reasonable therapeutic dosages of single agents. At the present time, most physicians initiate antianginal therapy using combinations of long-acting nitrates and β blockers. Instead of simply adding calcium-channel blockers to this regimen in patients with refractory symptoms, we prefer to substitute for the β blocker a heart-rate-lowering calcium-channel blocker (either verapamil or diltiazem) as single-drug therapy. There is ample evidence from controlled clinical trials to suggest that verapamil and diltiazem have at least equivalent therapeutic efficacy compared with β blockers in patients with chronic stable angina.[2,4,6,48,56] Moreover, in a given person, either one or the other class of drugs may be significantly more effective, lending credence to the proposal that each class should be tried individually before combination therapy is contemplated. Perhaps patients who preferentially respond to calcium-channel blockers are more susceptible to dynamic changes in coronary vasomotor tone as a contributing pathophysiologic mechanism of angina, whereas patients who respond to β blockers have fixed occlusive atherosclerotic disease as the dominant mechanism precipitating angina. After substitution calcium-channel blocker therapy is attempted, patients who remain symptomatic are candidates for combination therapy with β blockers. We recommend careful upward titration starting with relatively small doses of β blockers, so that heart rate and blood pressure responses are further blunted but dangerous drug-related adverse effects are minimized. This approach has the advantage of optimizing patient compliance and cost-effectiveness (by favoring single-drug therapy whenever possible), while reducing the possibility of harmful drug reactions.

Another approach that has gained much popularity in clinical practice involves the immediate addition of nifedipine to β blockers (and nitrates) in resistant patients. Although this prescribing pattern is generally safe and is simpler than substitution drug therapy, we find it somewhat less desirable; compliance is poorer, cost is greater and nifedipine–β-blocker combinations are probably less effective than verapamil or diltiazem–β-blocker combinations. Importantly, in patients with significant antecedent LV dysfunction or conduction system disease arising in slow-channel dominated tissues, combination calcium-channel blocker and β-blocker therapy is relatively contraindicated. If necessary, combination therapy in such patients should favor nifedipine rather than verapamil of diltiazem and would mandate close patient monitoring and follow-up.

There is little doubt that the use of calcium-channel blockers combined with β blockers may provide much needed therapeutic benefit in patients with refractory chronic stable angina. However, when used in routine clinical practice, such combinations must be treated with great respect and require that patients be carefully selected and closely observed.

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Use of Calcium Antagonists in Ventricular Dysfunction

MARTIN A. JOSEPHSON, MD, and BRAMAH N. SINGH, MD, PhD

Calcium antagonists are now widely used in a variety of cardiocirculatory disorders, many of which are associated with varying levels of depressed myocardial function. Thus, the hemodynamic effects of calcium antagonists in patients with normal as well as depressed ventricular function are clinically relevant. None of the 3 agents verapamil, nifedipine or diltiazem exerts significant negative inotropic effects in patients with relatively normal myocardial function, although increases in left ventricular end-diastolic pressure may occur with verapamil and possibly diltiazem. In a setting in which ischemia, hypertension or arrhythmias contribute to cardiac failure, all 3 agents may ameliorate myocardial decompensation if they reverse the precipitating causes. In patients with depressed myocardial function, the effects of diltiazem are not known; verapamil may depress myocardial function, especially if the ventricular filling pressure is increased. Nifedipine generally has little depressant action in this setting and usually improves cardiac function, especially if the sympathetic reflexes are intact. However, hemodynamic deterioration after nifedipine administration has been reported. Thus, the available data do not support the use of calcium antagonists as afterload-reducing agents in heart failure and suggest caution in the use of these agents in patients with impaired ventricular performance.

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As a pharmacodynamic and therapeutic concept, calcium antagonism has recently become an important framework by which the properties of a large and chemically heterogeneous group of compounds may be delineated.[1] Such compounds are now known to hold much promise in the management of a wide variety of cardiocirculatory disorders,[2–4] especially ischemic myocardial syndromes, hypertension, obstructive cardiomyopathies and certain forms of cardiac arrhythmias. In many of these disorders myocardial function is often compromised to a variable degree; thus agents that have a potentially depressant effect on cardiac muscle might aggravate the existing level of ventricular performance even in therapeutic doses and concentrations. By the very nature of their effect on the myocardial slow channel, calcium antagonists exert a negative inotropic action best demonstrated in isolated cardiac muscle.[5] These agents are also potent peripheral vasodilators; the impedance reduction that they thereby cause may variably offset their negative inotropic proclivity, permitting their relatively safe application in cardiovascular therapeutics. It is becoming increasingly clear, however, that different types of calcium antagonists differ significantly in this regard. Furthermore, the clinical experience that has accrued raises 2 significant issues regarding the safety of these drugs when used in patients with myocardial dysfunction. The first is the safety of these agents when they are used to treat patients with various cardiovascular disorders such as angina or coronary vasospasm in patients with reduced ventricular function. The second is the safety of these agents, by virtue of their afterload-reducing effects, in the treatment of patients with heart failure.

This report examines these issues with respect to verapamil, nifedipine and diltiazem and with particular attention to their net pharmacodynamic properties. Initially, the relevant pharmacologic similarities and differences among these compounds will be reviewed; then their hemodynamic actions in patients with preserved as well as reduced ventricular function will be discussed. The clinical significance of these observations is then explored.

Pharmacologic Considerations

The effects of calcium-channel blocking drugs on myocardial contractility differ significantly in isolated preparations compared with those in intact animals and man. In vitro experiments in which reflex activity is absent demonstrate that all 3 calcium antagonists available for clinical use in the United States exert a dose-dependent inhibition of myocardial contractility that is reversed either by increasing the extracellular concentrations of calcium, or by agents that augment

From the Department of Cardiology, Wadsworth Veterans Administration Hospital, and the Department of Medicine, UCLA School of Medicine, Los Angeles, California. This study was supported in part by grants from the Medical Research Service of the Veterans Administration and the American Heart Association, the Greater Los Angeles Affiliate.

Address for reprints: Martin A. Josephson, MD, Department of Cardiology 691/111E, Wadsworth Veterans Administration Hospital, Wilshire and Sawtelle Boulevard, Los Angeles, California 90073.

the transmembrane transfer of calcium ion.[6] The potency of various calcium antagonists in uncoupling excitation-contraction in isolated cardiac tissues correlates well with their negative inotropic propensity and their potency to inhibit the slow calcium channel. In this regard, on the basis of molar concentrations, nifedipine is the most potent, diltiazem the least, and verapamil has an intermediate range of potency.[5,7,8] The same rank order of potency has been found for these compounds with respect to their ability to relax smooth muscle cells in vitro and to dilate arteries and arterioles in intact animals and presumably in man. For example, nifedipine, a prototype of the dihydropyridine subgroup of calcium antagonists, is the most potent for reducing systemic vascular resistance, an effect that is likely to be accompanied by marked reflex increases in heart rate and cardiac pump function.[9] The latter is particularly striking with nifedipine, because this drug has no significant primary depressant effect on sinoatrial (SA) nodal automaticity or myocardial function in intact animals and man. In contrast, verapamil and diltiazem have less marked peripheral vasodilator effects and often exhibit significant direct depressant effects on SA nodal automaticity. This, in turn, tends to attenuate the myocardial contractility and reflex increases in heart rate and myocardial performance that result from the peripheral dilator effects of verapamil and diltiazem. Thus, based on pharmacologic considerations, somewhat greater negative inotropic effects with verapamil and diltiazem might be expected than with the dihydropyridine type of calcium antagonists.

Hemodynamic Effects of Calcium Antagonists in Patients Without Significant Impairment of Ventricular Function

The pharmacologic and clinical considerations just outlined suggest that the net hemodynamic effects of calcium antagonists in patients with heart disease are likely to be the result of a complex interplay of simultaneous alterations in ventricular preload, afterload, myocardial contractility, coronary blood flow and heart rate, variably modulated further by the level of intrinsic ventricular function, the status of the autonomic nervous system, the presence or absence of myocardial ischemia and the properties of the various calcium antagonists themselves.[10,11] The characterization of the hemodynamic profiles of nifedipine, verapamil and diltiazem in patients with relatively well-preserved ventricular function permits a comparison of their effects in patients with reduced ventricular performance.

Nifedipine: When administered either intravenously or sublingually, nifedipine produces the most profound vasodilatation in the periphery; this leads to reflex increases in cardiac pump function in the setting of both normal and impaired ventricular function. For example, a 20-mg sublingual dose of nifedipine was found to increase cardiac index (18%) with corresponding directional changes in heart rate and the first derivative of left ventricular pressure (dP/dt_{max}).[12] Reflex augmentation of myocardial function after this dose administration was also documented by an accompanying increase in the left ventricular (LV) ejection fraction (9%) and the mean velocity of circumferential fiber shortening (35%). These changes occurred without alterations in end-diastolic pressure or end-diastolic volume.[12] We emphasize, however, that while nifedipine clearly does not depress myocardial function in most patients, its safety in this regard is largely due to its potent peripheral vasodilator action, which lead to ventricular unloading and activation of sympathetic reflexes. These effects nullify and even reverse nifedipine's intrinsic negative inotropic actions. However, if the reflex effects were attentuated either by disease or concomitant use of sympatholytic drugs, significant depressant effects of the compound are likely to become apparent.

Verapamil: Numerous investigators have studied the hemodynamic effects of intravenously administered verapamil in patients with cardiac disease,[13–15] and data have also appeared recently (discussed later) on diltiazem.[16] Figure 1 illustrates the typical hemodynamic

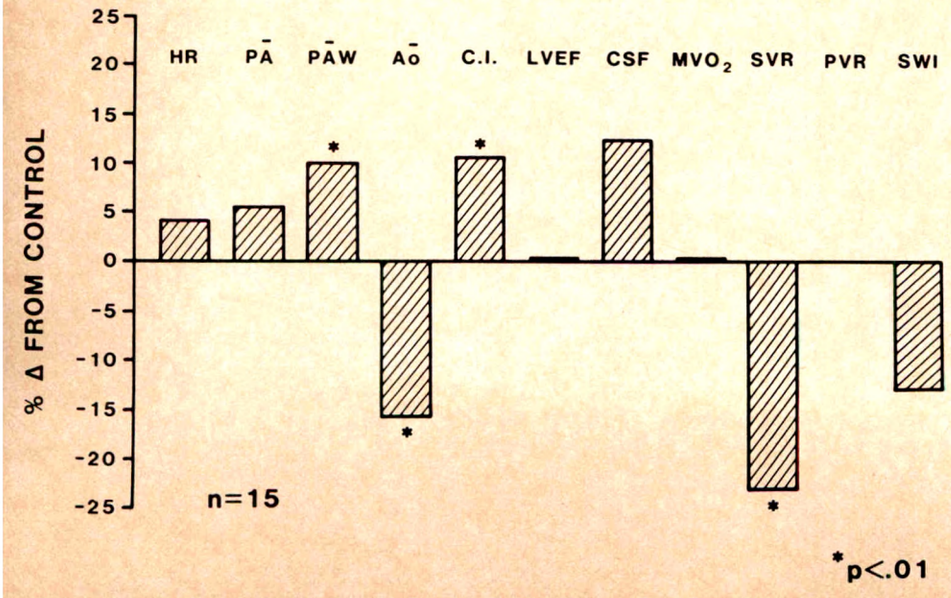

FIGURE 1. Effects of intravenous verapamil on systemic and coronary hemodynamic features and left ventricular ejection fraction in 15 patients with coronary artery disease. $A\bar{o}$ = mean aortic pressure; CI = cardiac index; CSF = coronary sinus flow; HR = heart rate; LVEF = LV ejection fraction; $M\dot{V}O_2$ = myocardial oxygen consumption; $P\bar{A}$ = mean pulmonary artery pressure; $P\bar{A}W$ = mean pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; SWI = stroke work index.

changes produced by the administration of intravenous verapamil (0.145 mg/kg bolus injection followed by 0.005 mg/kg/min continuous infusion) in a series of 15 patients with chronic stable angina undergoing diagnostic cardiac catheterization.[15] This group of patients had relatively preserved ventricular function with a mean ejection fraction of 56%. In this study, the 23% decrease in systemic vascular resistance and 16% decrease in mean arterial pressure document the peripheral vasodilator effect of verapamil. Despite the 11% increase in cardiac index, the associated 10% increase in the pulmonary capillary wedge pressure and a 13% decrease in the stroke work index undoubtedly reflect the intrinsic myocardial depressant effect of verapamil. This is supported by the findings of Singh and Roche,[13] which showed that 10 mg of verapamil given intravenously to patients with cardiac disease led to an approximately 10% decrease in the LV dP/dt_{max}. The hemodynamic findings reported by Chew et al[15] and Singh and Roche[13] are very similar to those described by Ferlinz et al[14] insofar as these investigators found a modest increase in the filling pressures of the ventricles. However, Ferlinz et al found a small but apparently significant increase in LV ejection fraction using contrast left ventriculography; in contrast, Chew et al from our laboratory reported no change, using radionuclide ventriculography. It is conceivable that the difference between the 2 reports may reflect differences in patient populations as well as the differing methods used to determine LV ejection fraction. It is also possible that an increase in LV ejection fraction might occur after the administration of verapamil in some patients if the drug were given at a time active ischemia were present, with an improvement in the degree of myocardial ischemia contributing to the improved ejection fraction. An improvement in LV ejection fraction after administration of verapamil was demonstrated in patients in whom a decrease in this parameter was induced by rapid atrial pacing[17] or by supine bicycle exercise;[18] these maneuvers are known to produce ischemia and impair ventricular function in the setting of coronary artery disease. Such observations emphasize that in the setting of myocardial ischemia antianginal drugs such as verapamil are likely to improve rather than depress ventricular ejection fraction.

Diltiazem: The data from our laboratory on the hemodynamic effects of intravenously administered diltiazem (0.16 to 0.25 mg/kg bolus injection) are summarized in Figure 2. The group of patients studied had coronary artery disease and clinical characteristics similar to those reported in our study with verapamil.[15] The mean LV ejection fraction for the diltiazem group was also similar, averaging 63%. The 22% decrease in systemic vascular resistance, the 12% decrease in mean arterial pressure and the 8% increase in the cardiac index associated with a small but not statistically significant decrease in the stroke work index resemble the changes after verapamil administration. Neither agent produced significant changes in heart rate, but a modest increase in the mean capillary wedge pressure occurred with diltiazem as we[16] found in the case of verapamil. These data suggest a mild degree of impairment of ventricular function. As with the intravenous administration, neither verapamil[18] nor diltiazem[19] given on a long-term oral basis was found to significantly depress LV ejection fraction in patients with coronary artery disease who have relatively well-preserved ventricular ejection fraction.

When the overall data on the hemodynamic effects of verapamil, nifedipine and diltiazem in patients with relatively well-preserved ventricular ejection fraction are considered in light of the aforementioned data, the negative inotropic effects of these agents, clearly evident in isolated cardiac muscle, are almost completely balanced by their afterload-reducing properties. Thus, when given on either a short-term basis by the intravenous route or on a long-term basis by mouth, the use of these agents is unlikely to be accompanied by clinically significant depression of myocardial function. In general, this is consistent with clinical experience. However, as indicated earlier, there are clinical situations in which these agents might be expected to exert a potentially depressant effect on cardiac performance (discussed later).

Effects of Calcium Antagonists in Acute Myocardial Infarction

Only limited data are available on the effects of calcium antagonists in patients with acute myocardial infarction. However, intravenous doses of verapamil

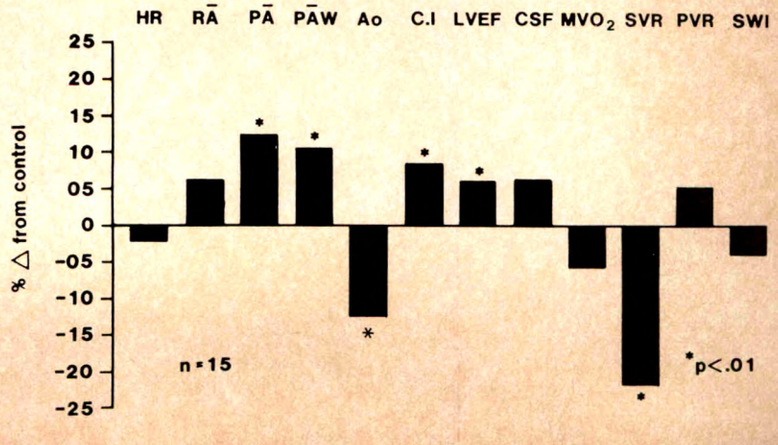

FIGURE 2. Effects of intravenous diltiazem on systemic and coronary hemodynamic features and left ventricular ejection fraction in patients with coronary artery disease. RĀ = right atrial pressure. Other abbreviations as in Figure 1.

(0.145 mg/kg as a bolus injection followed by 0.005 mg/kg/min continuous infusion) in patients with uncomplicated myocardial infarction produced hemodynamic effects identical to those in patients with relatively normal LV ejection fraction undergoing diagnostic catheterization for the evaluation of coronary artery disease.[15] Of particular interest was the observation that in both subsets of patients the drug had no depressant effect on LV ejection fraction determined either by contrast or radionuclide ventriculography. Comparable data for nifedipine or diltiazem given parenterally to patients with acute myocardial infarction are not available at present. However, all 3 drugs were investigated by Theroux et al[20] in patients with uncomplicated acute myocardial infarction given single oral doses of the respective agents. The mean data are summarized in Figure 3, which emphasizes the somewhat differing pharmacologic effects of the 3 compounds. For example, heart rate after nifedipine increased by 6%, decreased by 11% after diltiazem and remained unchanged after verapamil administration. After nifedipine, the mean arterial pressure decreased by 12% compared with a 6% decrease after diltiazem, while the decrease for verapamil was intermediate in magnitude. It is noteworthy that cardiac index did not change significantly in any of the 3 groups, although there was a trend for it to increase after nifedipine. As discussed earlier, the differences in the effects of these compounds on heart rate and systemic vascular resistance reflect their differing interactions with the autonomic nervous system and their varying potencies as peripheral vasodilators. Furthermore, the data relative to heart rate changes suggest that when a calcium antagonist must be given to a patient with ischemia, but with bradycardia also, nifedipine might be preferable to the other 2 compounds. However, the data do not permit conclusions regarding the patterns of hemodynamic changes that may be found with these compounds in patients with various LV dysfunctions and after long-term therapy. The limited data that are available are discussed later.

Calcium Antagonists in the Setting of Ventricular Dysfunction and Hypertensive Crises

When LV dysfunction occurs as a result of myocardial ischemia or other causes (for example, hypertensive crises) that may respond to calcium antagonists, beneficial effects might result from the use of these agents. In other instances the response may be unpredictable, varying from a depressant one to an improvement in ventricular performance, depending on the properties of an individual calcium antagonist and the overall clinical situation.

Nifedipine: In a study involving 15 patients with stable angina and a mildly decreased LV ejection fraction of 49%, which decreased to 42% with exercise, 20 mg of oral nifedipine resulted in improved resting and exercise ejection fractions (52% and 47%, respectively).[21] Additionally, segmental wall motion determined by radionuclide ventriculography and myocardial perfusion evaluated by thallium-201 scintigraphy were improved. During pacing-induced ischemia, nifedipine

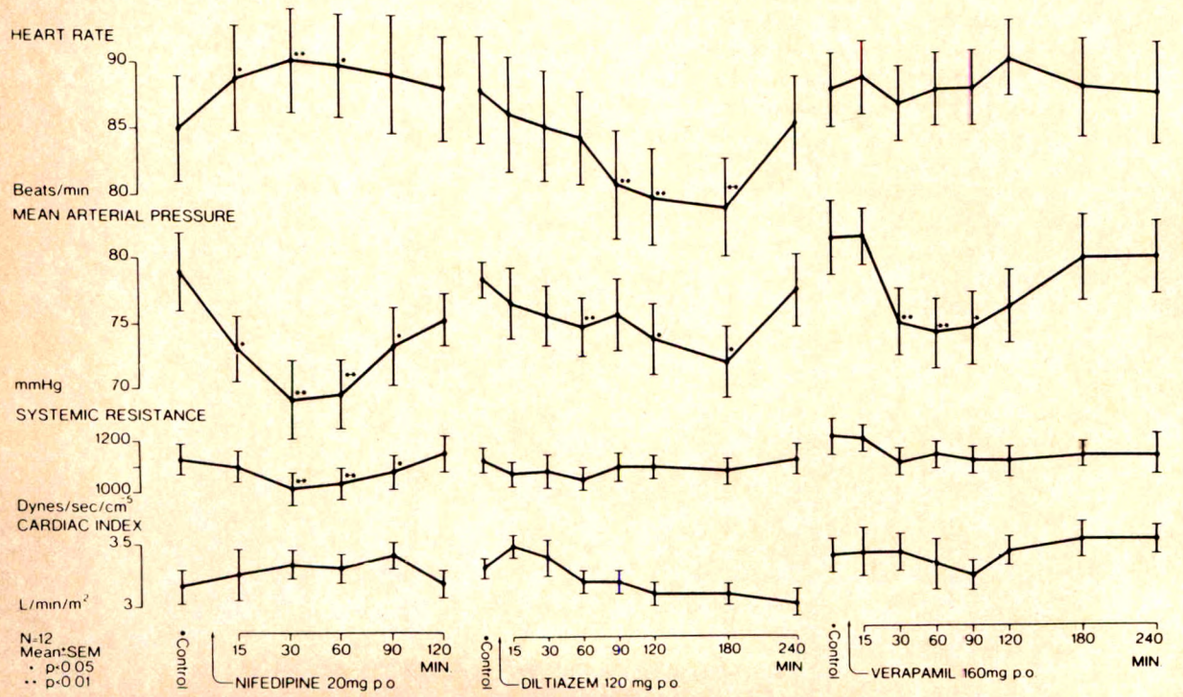

FIGURE 3. Comparative effects of single doses of 3 calcium antagonists in patients with recent acute myocardial infarction. The data shown are mean ± standard deviation (adapted from Theroux et al[18]). Note that nifedipine produces most profound decrease in arterial pressure with reflex increases in heart rate. Effect is least with diltiazem, which *decreases* heart rate; effect of verapamil is intermediate between 2 other compounds. PO = orally; SEM = standard error of the mean.

permitted pacing to higher heart rates before the onset of angina,[22] an effect probably due to the decrease in the myocardial oxygen demands rather than to an increase in myocardial flow. These overall data on the effects of nifedipine on ventricular dysfunction induced by myocardial ischemia emphasize the fact that the beneficial effect of the calcium antagonist on ventricular function is an indirect one mediated through the amelioration of ischemia, an effect that might be expected to occur with all effective antianginal or antiischemic compounds. A similar "indirect" beneficial effect has been demonstrated in hypertensive patients[23–25] given sublingual or oral doses of nifedipine. A similar effect with oral doses of the drug has been reported to persist during 3 weeks of long-term therapy.[24] It is noteworthy that in 10 patients with hypertensive crisis (blood pressure >220/120 mm Hg), all achieved an acceptable hypotensive response after nifedipine administration.[25] In patients in heart failure in this same study, pulmonary edema was promptly relieved by nifedipine. Similarly, Guazzi et al[24] reported that 3 patients with acute left-sided heart failure caused by hypertension had significant improvement after 10 mg doses of nifedipine were given at intervals of 1 hour. Significant decreases in systemic and pulmonary arterial pressures associated with increases in cardiac output accompanied the clinical improvement effected by nifedipine. Further documentation of the beneficial effect of nifedipine in this setting was provided by Polese et al[26] in 7 patients with congestive heart failure complicating severe hypertension. Nifedipine was given 10 mg sublingually. A significant decrease in both systolic and diastolic internal ventricular dimensions measured echocardiographically followed the administration of nifedipine; there was also improvement in the mean velocity of circumferential fiber shortening and in the left and right ventricular ejection phase indexes. Similar findings in patients with various degrees of LV dysfunction were demonstrated by Ludbrook et al[12] after 20-mg sublingual doses of nifedipine. In this study, a significant decrease in LV preload and end-diastolic pressure was seen only in those patients with increased LV end-diastolic volumes ≥90 ml/m^2. It was in this group of patients with more marked ventricular dysfunction that the most striking decrease in systemic and pulmonary vascular resistance and significant increase in cardiac index occurred.

We emphasize that the use of nifedipine in the setting of cardiac failure, whether overt or latent, may not always be free of adverse effects. For example, Brooks et al[27] reported clinical deterioration, that is, development of severe hypotension, in 2 patients with severe congestive cardiac failure after nifedipine. In these patients, although the pulmonary capillary wedge pressure was decreased by nifedipine, cardiac index decreased markedly and calcium plus epinephrine administration was necessary to restore adequate cardiocirculatory function. It must be assumed that in certain subsets of patients with cardiac failure, the reflex mechanisms activated by peripheral dilatation after nifedipine are inadequate to offset the intrinsic negative inotropic effects of the calcium antagonist.

Verapamil: Although verapamil has been evaluated more extensively than diltiazem in patients with myocardial dysfunction, adequately controlled data in a similar clinical subset of patients are also limited. In sharp contrast to verapamil's lack of adverse hemodynamic effects in patients with normal or near normal ventricular performance, Chew et al[15] found clinical and hemodynamic deterioration in a small number of patients with severely decreased LV ejection fraction (<35%) and increased pulmonary capillary wedge pressure (>18 mm Hg) after intravenous verapamil (0.145 mg/kg given as a bolus injection followed by continuous infusion at 0.005 mg/kg/min). Chew's findings, however, conflict with those from Ferlinz et al.[28] The differences between the hemodynamic effects of verapamil in patients with depressed ventricular function and increased wedge pressures and those without these resting abnormalities are illustrated in Figure 4.

On the basis of these results, it would appear unjustified to use verapamil as an afterload-reducing agent in the setting of ventricular dysfunction rather than the conventional impedance-reducing agents. However, this use of verapamil needs to be distinguished from its use in influencing ventricular dysfunction through an indirect means. For example, as with nifedipine and other

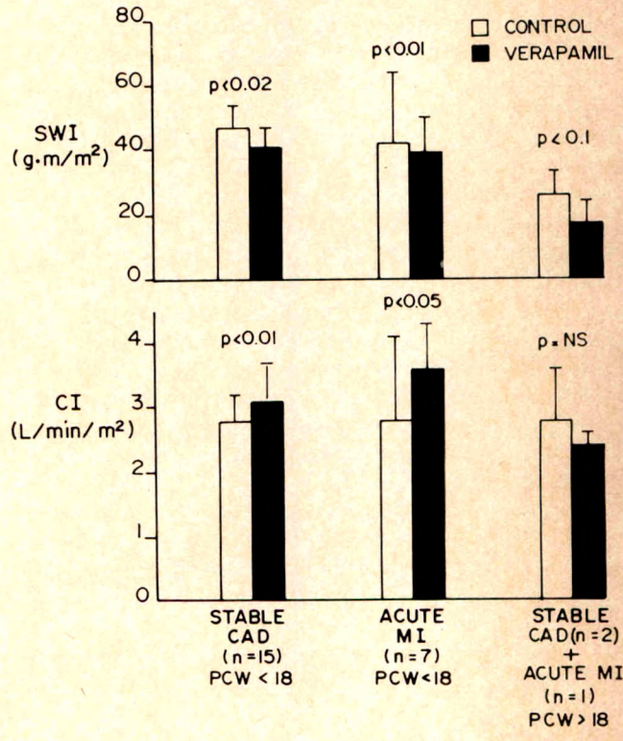

FIGURE 4. Effects of verapamil (0.145 mg/kg intravenously, followed by intravenous infusion of 0.005 mg/kg/min) on stroke work index (SWI) and cardiac index (CI) in patients with varying levels of mean pulmonary capillary wedge pressure (PCW). In patients with significantly increased mean wedge pressure (>18 mm Hg), SWI is significantly decreased by verapamil. In these patients, increases in mean wedge pressure may lead to abrupt clinical deterioration (based on data from Chew et al[13]). CAD = coronary artery disease; MI = myocardial infarction.

calcium antagonists, verapamil has been shown to exert beneficial effects in patients with ventricular dysfunction resulting from myocardial ischemia induced either by exercise[18] or atrial pacing.[19] Similarly, when cardiac failure is either produced or aggravated by development of dysrhythmias responsive to intravenous verapamil, use of the drug in such patients is likely to be associated with improvement rather than deterioration in hemodynamic and ventricular function. Under these circumstances, the hemodynamic improvement that follows the slowing of the heart rate outweighs verapamil's potentially negative inotropic effects.[29] In this context, it is of interest that although most of the patients treated with verapamil for supraventricular tachyarrhythmias by Schamroth et al[30] were in heart failure, an excellent clinical outcome was almost uniformly obtained. Nevertheless, even in this setting caution is warranted because the reversal of an arrhythmia by verapamil is not invariable and profound cardiac depression may result in the absence of a prompt antiarrhythmic response. This is particularly likely in the case of wide QRS tachycardia, a setting in which a ventricular tachycardia may be erroneously mistaken for a supraventricular tachycardia with aberrant conduction.

On theoretical grounds, another clinical situation in which verapamil and other calcium antagonists might be of benefit in the setting of cardiac decompensation is hypertensive heart disease. Although verapamil has been used to control hypertension in patients with angina pectoris,[31] data on the drug's efficacy and safety in the setting of heart failure complicating accelerated hypertension are limited.[32] In one study by Guazzi,[23] 2 hypertensive patients without previous history of heart failure who received verapamil 160 mg orally 3 times daily had paroxysmal nocturnal dyspnea requiring digoxin and diuretics for the control of the resulting heart failure.

Diltiazem: Diltiazem, the least negatively inotropic calcium antagonist in studies of isolated tissues and intact animals,[33] has not been investigated systematically in patients with varying levels of ventricular dysfunction. In our studies of diltiazem in patients with pacing-induced myocardial ischemia,[16] the drug attenuated the decrease in the LV ejection fraction produced by coronary sinus pacing. Under resting conditions, the mean LV ejection fraction was 63%, decreasing to 53% (<0.01) after pacing; diltiazem pacing at an identical heart rate resulted in an ejection fraction of 59%, which was not significantly greater than the pacing value before diltiazem. However, only 1 of 15 patients in the series had significantly decreased LV ejection fraction. In this patient, the ejection fraction of 45% decreased to 42% during atrial pacing; after diltiazem at an identical pacing rate, the ejection fraction decreased to 32%. This decrease was unexplained; in most other patients the expected decrease in the ejection fraction was attenuated by diltiazem. Such a decrease in the ejection fraction, however rare, indicates that diltiazem has the potential to depress myocardial performance. Nevertheless, the intravenous data for the most part are in agreement with the observations after the long-term administration of the drug to patients undergoing treadmill exercise.[19] For example, in 13 patients with coronary artery disease, the LV ejection fraction decreased 15% (from 52 to 44%) during exercise while the patients were taking placebo; in contrast, during diltiazem administration, the corresponding decrease was 10% (58 to 52%), with the resting baseline value being higher than that before the drug was given. Thus at an identical workload, the LV ejection fraction of 52% was significantly greater than the 44% obtained during the placebo phase of the study. In this series, only 3 of the 13 patients had resting LV ejection fractions of <45% (range 31 to 45%), with a mean of 37%. With exercise during placebo administration, it decreased to 32% (−13.5%). With diltiazem before exercise, the LV ejection fraction increased to 43% (+16.2%); with exercise with diltiazem, the corresponding decrease (43 to 34%) of 20.9% was thus higher than that for the entire group of 13 patients in whom the mean LV ejection fraction of 58% with diltiazem at rest decreased to 52% with exercise (a decrease of 10.3%). Thus, although diltiazem may exert a beneficial effect on LV ejection fraction during ischemia, these preliminary data in small numbers of patients suggest that such a salutary effect may be less apparent in the subset of patients with significant ventricular dysfunction. In experimental heart failure after long-term volume loading in the dog,[34] diltiazem has been found to exert significant myocardial depressant effects. A similar depressant effect was not demonstrable for the frequently used afterload-reducing agent nitroprusside, emphasizing the essential difference between conventional impedance-reducing agents and calcium antagonist drugs.

The aforementioned data suggest that ventricular dysfunction resulting from myocardial ischemia may be lessened by the administration of diltiazem. This effect is undoubtedly due in part to the calcium antagonist's favorable effect on the determinants of myocardial oxygen consumption, and, as suggested by data from experimental studies on regional blood flow,[35] possibly on myocardial perfusion as well.

Calcium Antagonists as Afterload-Reducing Agents

The available data on verapamil discussed earlier and the theoretical considerations, as well as anecdotal experience and a preliminary study with diltiazem in a small series of patients with cardiac failure,[36] do not establish the role of these agents in congestive failure. The clinical utility of either compound as an afterload-reducing agent solely for the treatment of cardiac failure caused by irreversibly impaired ventricular function is limited. This question is not yet clearly answered for nifedipine and the newer dihydropyridines. A number of uncontrolled studies with nifedipine in cardiac failure of various origins, although indicating that beneficial hemodynamic effects may follow in some patients, especially over the short term, do not clearly support the use of nifedipine as a primary afterload-reducing agent. In the short-term study by Polese et al,[26] 7 patients with congestive heart failure caused by primary myocardial disease with a mean capillary wedge

pressure of 39 mm Hg, a significant decrease in the pulmonary wedge pressure to 26 mm Hg and an improvement in cardiac index and other indexes of ventricular performance were observed. In this context the data of Elkayam et al[37,38] on the short-term hemodynamic effects of orally administered nifedipine in 32 patients with severe congestive heart failure are of interest. The effects reported were variable, unpredictable and often adverse. For example, although nifedipine functioned as a powerful arterial dilator, often producing an increase in cardiac index, 10 of 32 patients did not respond and 4 developed severe hemodynamic deterioration. Furthermore, the potentially unfavorable effect of nifedipine could not be predicted from baseline hemodynamic features or the LV ejection fraction. Their data cast serious doubt on the role of nifedipine as an afterload-reducing agent in patients with severe chronic congestive cardiac failure.

The subset of patients with cardiac failure that might benefit from the administration of nifedipine is the one with primary valvular regurgitation associated with relatively preserved ventricular ejection function. For example, in patients with aortic and mitral regurgitation and pulmonary edema, single sublingual doses of nifedipine were reported to produce clinical improvement accompanied by decreases in pulmonary wedge pressures and circumferential wall stress, and increases in circumferential fiber shortening, the mean rate of ejection and cardiac index.[26] In patients with chronic congestive cardiac failure (mean LV filling pressure of 19 mm Hg), the hemodynamic improvement after nifedipine appeared to be demonstrable most readily in those with mitral regurgitation,[39] an entity in which afterload reduction by whatever means has been shown to be of much clinical utility. It is noteworthy that in the study by Cantelli et al[39] in this setting, the addition of digoxin plus nifedipine resulted in an even greater augmentation of cardiac performance than with nifedipine alone. We emphasize that although these preliminary, limited data with nifedipine as an afterload-reducing agent in a particular subset of patients with cardiac failure are encouraging, the effects of the drug in this regard must be compared stringently with those of conventional impedance-reducing agents devoid of intrinsic negative inotropic propensity. Only then will the precise role of the dihydropyridine group of calcium antagonists as afterload-reducing agents in the control of chronic congestive heart failure be clearly defined. For the present, the available data indicate that such a role is likely to be limited.

Therapeutic Implications

The data discussed herein suggest that, in patients with relatively preserved ventricular function, the potential intrinsic depressant effect of calcium antagonists is nullified or even reversed by their potent vasodilator actions. With nifedipine, a positive inotropic effect may be seen in association with varying degrees of tachycardia. A significant but clinically negligible degree of negative inotropic effect may be seen with diltiazem and verapamil.

Of the 3 calcium antagonists discussed in this article, the hemodynamic profile of nifedipine appears to be the most favorable for use in patients with depressed ventricular function. However, a clear distinction needs to be made between using this compound to treat a clinical situation for which this class of drugs is normally indicated in a patient with depressed ventricular function, and using it solely to improve cardiac failure by impedance reduction.

In patients with significantly depresed LV function, especially with increased LV filling pressures, clinical deterioration may supervene in a good proportion; such an effect is less likely to occur with nifedipine unless sympathetic reflexes are blocked. However, when heart failure is due to ischemia or hypertension, reversal of these functional abnormalities is likely to lead to improvement rather than deterioration in myocardial function. Similarly, cardiac failure aggravated by tachyarrhythmias is likely to be alleviated if these drugs (especially diltiazem or verapamil) lead to a prompt termination of arrhythmia. Whether calcium antagonists may be used for the purposes of afterload reduction in patients with congestive heart failure is not clear. At least in the case of nifedipine, it has been found that in certain subsets of patients, hemodynamic function may be improved during short-term administration. In others, however, cardiac failure may be aggravated. The overall data do not indicate that, as a class, calcium antagonists are likely to represent an important advance as impedance-reducing agents. Their use in most patients is not accompanied by a significant deterioration in ventricular function, but heart failure may be aggravated in those with severely decreased LV ejection fraction. We recommend caution with respect to the choice of an individual agent as well as the route and dose of drug administration in patients with compromised ventricular performance.

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Slow Inward Current and Cardiac Arrhythmias

ROBERT F. GILMOUR, Jr., PhD, and DOUGLAS P. ZIPES, MD

The slow inward current contributes to the normal electrical and contractile activity of several cardiac and vascular tissues and also may mediate the electrical abnormalities responsible for certain cardiac arrhythmias. The slow inward current differs from the fast inward sodium current in that it is carried primarily by calcium rather than sodium, requires a more positive level of membrane potential to be activated, has slower activation and inactivation kinetics, is responsible for normal depolarization in sinus and atrioventricular (AV) nodal cells and is blocked by a rather specific group of agents that includes verapamil, diltiazem and nifedipine. Recent data suggest that slow-channel openings occur in bursts, separated by silent periods, and that less negative membrane potentials and beta-adrenergic stimulation increase the probability that the channels will open. Inactivation of the channels is associated with a lower probability of channel opening. Slow-channel blocking agents such as verapamil, diltiazem and nifedipine appear to bind to activated, rather than rested, slow channels. Therefore, their effects are more prominent at faster pacing rates and at less negative membrane potentials. Clinically occurring cardiac arrhythmias dependent on the slow inward current include primarily sinus and AV nodal reentry and reciprocating tachycardia in the Wolff-Parkinson-White syndrome when one of the pathways incorporates the AV node. Damaged atrial, ventricular and specialized tissue also can generate slow response-mediated reentry or forms of automaticity that may be clinically important under certain circumstances.

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The slow inward current contributes to the normal electrical and contractile activity of several cardiac and vascular tissues and also may mediate the electrical abnormalities responsible for certain cardiac arrhythmias. Abnormalities involving the peripheral and coronary vasculature can affect the genesis of arrhythmias indirectly, whereas abnormalities involving pacemaking, specialized conducting and working myocardial tissues affect the genesis of arrhythmias directly. In this report, we summarize present knowledge concerning the electrophysiologic characteristics of the slow inward current, its modulation by autonomic nervous system neurotransmitters, and its role in cardiac action potential generation and propagation under physiologic and pathophysiologic conditions. We then discuss the possible participation of the slow inward current in the genesis of some cardiac arrhythmias and the therapeutic indications, efficacy and possible mechanism of action of slow-channel blocking agents.

From the Krannert Institute of Cardiology, the Departments of Pharmacology and Medicine, Indiana University School of Medicine, and the Roudebush Veterans Administration Medical Center, Indianapolis, Indiana. This study was supported in part by the Herman C. Krannert Fund, Indianapolis, Indiana, by Grants HL-06308, and HL-07182 from the National Heart, Lung and Blood Institute, the National Institutes of Health, Bethesda, Maryland, by the Attorney General of Indiana Public Health Trust, by the Roudebush Veterans Administration Medical Center, Indianapolis, Indiana, and by a Grant-In-Aid from the American Heart Association, Indiana Affiliate, Inc., Indianapolis, Indiana.

Address for reprints: Robert F. Gilmour, Jr., PhD, Krannert Institute of Cardiology, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46223.

Characteristics of the Slow Inward Current

After the first recordings of transmembrane potentials in cardiac tissue,[1,2] Noble[3] constructed a mathematical model that reproduced the time course of Purkinje fiber action potentials. He assumed that changes in transmembrane potential were due to voltage- and time-dependent alterations in specific membrane conductances to sodium (depolarization) and potassium (repolarization), much as Hodgkin and Huxley[4] had shown previously for the action potential of the squid giant axon. However, other investigators demonstrated that action potential amplitude and duration in guinea pig ventricle were unchanged by lowering extracellular sodium ion concentration ($[Na^+]_o$)[5,6] and the upstroke and plateau phases of various cardiac action potentials could be dissociated in several ways.[7,8] These reports suggested that the currents responsible for the cardiac action potential differed qualitatively, as well as quantitatively, from those previously described in nerve.

Reuter[9] strongly supported this suspicion by demonstrating directly the existence of an inward calcium current in Purkinje fibers using a voltage clamp technique. This current differed from the previously described fast inward sodium current in that it required a more positive level of depolarization to be activated, remained activated for a longer period of time, was not blocked by the sodium-channel blocker tetrodotoxin, depended on the extracellular calcium concentration and had a reversal potential near the expected calcium equilibrium potential. Subsequently, these results have been confirmed by other investigators. It has been proposed that current flow through the slow channel, like that through the fast channel, is regulated by a series of activation and inactivation gates that open and close in response to changes in the transmembrane potential and time, although the actual values for the voltage- and time-dependency of the fast and slow inward currents differ markedly. At a normal resting membrane potential, the slow-channel activation gates are completely closed and the inactivation gates are completely open (Fig. 1). After depolarization of the membrane to a threshold potential, the activation gates open rapidly and the inactivation gates slowly close. Before complete closure of the inactivation gate, current flows through the slow channel. Upon return to the resting potential during diastole, the activation gate rapidly closes while the inactivation gate slowly opens, a process referred to as recovery from inactivation, or reactivation.

Although this scheme has been supported by numerous voltage clamp studies in multicellular preparations, recent experiments in which single calcium channels were studied using a patch clamp technique[10–12] suggest that descriptions of slow-channel activation and inactivation kinetics based on the formulations developed by Hodgkin and Huxley for fast sodium channels may not be appropriate. These experiments indicate that individual calcium channels have a mean open time of approximately 1 ms and that channel openings occur in bursts separated by silent periods. At membrane potentials near threshold, the bursts may occur almost at random and there is a latency between the onset of the clamp and the occurrence of the initial burst. As the clamp potential is made less negative, channel openings tend to occur sooner after the onset of the clamp, and the probability that the channels will open increases, as does the mean burst duration. However, the open time of individual channels is only slightly prolonged and the single channel current magnitude per opening decreases. "Inactivation" of the channels is associated with a lower probability of channel opening, rather than a decrease in current magnitude through those channels that do open. The latency preceding the first channel opening and the bursting patterns of the channels suggest that the calcium channel may cycle through several closed states before opening, in contrast to the first order open-closed reaction typified by the Hodgkin and Huxley scheme.

The threshold potential for activation of the slow inward current generally is from −50 to −35 mV, compared with a threshold potential of −70 to −55 mV for the fast inward sodium current.[13] Therefore, the slow inward current is activated in a membrane potential range at which the fast inward sodium current is largely inactivated. This implies that action potentials ("slow responses") can occur in partially depolarized cells in which the fast sodium channels have been inactivated, provided conditions are appropriate for normal slow channel activation.

It has been estimated that the fast inward sodium current lasts less than 2 ms.[14] Although individual slow channels also appear to open and close rapidly, as discussed previously, the mean current flowing through all of the slow channels in a given cell has a much slower time course, because not all of the slow channels open immediately upon depolarization of the membrane. Rather, some of the slow channels open soon after the membrane is depolarized, whereas others open later. When the currents flowing through the individual channels are averaged over the course of a depolarizing voltage clamp step, the apparent activation of the slow inward current takes from 10 to 20 ms. "Inactivation" may take 50 to 500 ms, depending on the membrane potential,[13] and reactivation takes 2 to 10 times longer than reactivation of the fast sodium channel. Thus, the total slow inward current has a slower onset than the fast inward sodium current, flows for a longer period of time and requires more time after a stimulus to be fully reactivated.

The slow inward current is often referred to as the slow inward calcium current, because the slow channel has been shown to be selectively (but not exclusively) permeable to calcium in various cardiac tissues[15–18] and the calcium-dependence of slow channel current was originally used as one of the discriminating criteria to separate the fast and slow inward currents.[9] Even though the slow channels may be 70 to 100 times more permeable to calcium than to sodium,[17,18] sodium may account for nearly one third of the slow inward current in certain instances, due to the much higher extracellular concentration of sodium versus calcium.

Slow channel current may be carried by other divalent cations, such as barium, strontium, magnesium and manganese,[19–21] although manganese primarily inhibits slow channels in most species. The divalent cations cobalt[20] and nickel[20] and the trivalent cation lanthanum[22] inhibit the slow inward current without being charge carriers themselves. Along with manganese, these latter cations are often used as relatively specific inhibitors of the slow inward current, because they have minimal effects on the fast inward sodium current, although they may have significant direct and indirect effects on outward potassium currents.

Pharmacologic agents such as (−) verapamil[23], its methoxy derivative D-600,[23–25] nifedipine[26,27] and diltiazem[28] can selectively inhibit the slow inward current. The blocking effects of verapamil, D-600 and diltiazem are most apparent at high rates of stimulation and at less negative membrane potentials, implying that these drugs bind to their receptors when the channel is in the open configuration[28,29] and remain bound as the channel inactivates. In contrast, dihydropyridine derivatives

such as nifedipine have been reported to reduce slow-channel conductance without affecting activation or inactivation kinetics.[26] More recent studies have shown, however, that the slow channel blocking effects of the dihydropyridine derivatives are membrane potential-dependent and are more marked at higher stimulation frequencies.[27]

Modulation of the Slow Inward Current by Autonomic Nervous System Neurotransmitters

Neurotransmitters of both the sympathetic[31,32] and parasympathetic[33–35] nervous system modulate the activity of slow channels, as reflected by changes in the slow inward current measured by voltage clamp and by indirect indexes of the slow inward current, such as the configuration of slow channel–dependent action potentials, contractile force, and sinus nodal automaticity and atrioventricular (AV) nodal conduction.

Beta-adrenergic agonists are thought to bind to specific sarcolemmal receptors and activate adenylate cyclase, producing an increase in intracellular levels of adenosine 3′:5′-cyclic monophosphate (cyclic AMP).[36,37] Cyclic AMP activates a cyclic AMP-dependent protein kinase that catalyzes the phosphorylation of specific membrane proteins controlling the permeability of the slow channel, thereby increasing either the number of slow channels available for activation after an appropriate level of depolarization or the probability that an individual channel will be open at any given voltage[11] (Fig. 1). Phosphatase-mediated dephosphorylation and the conversion of cAMP to 5′-AMP by phosphodiesterase deactivates the slow channels. Consequently, inhibition of phosphodiesterase activity increases cyclic AMP levels and the slow inward current.

This scheme is supported by the observations that the slow inward current is increased by catecholamines,[38–40] the lipid soluble dibutyryl derivative of cyclic AMP,[38,39] intracellular application of the catalytic subunit of protein kinase[41] and the phosphodiesterase inhibitor theophylline.[42] In addition, these agents increase the plateau phase of the cardiac action potential,[43,44] increase contractile force,[32,45] produce a positive chronotropic response[46] and restore excitability to cardiac tissues depolarized by high extracellular potassium.[32,47] Agents such as isoproterenol most likely enhance slow channel current by increasing the probability that the channel will open after membrane depolarization, rather than by altering the magnitude of current flowing through the channel.[11]

Muscarinic cholinergic agonists directly inhibit the slow inward current in atria and papillary muscle, as measured by the voltage clamp technique.[34,48] In addition, acetylcholine antagonizes the electrophysiologic effects of β-adrenergic stimulation in ventricular muscle[49] and Purkinje fibers,[33] although it is uncertain whether these effects are due solely to inhibition of the slow inward current. The effects of acetylcholine on the slow inward current may be mediated by an increase in the intracellular concentration of cyclic guanosine monophosphate (GMP), as suggested by an association between increased cyclic GMP levels and decreased force development[50] and shortening of action potential

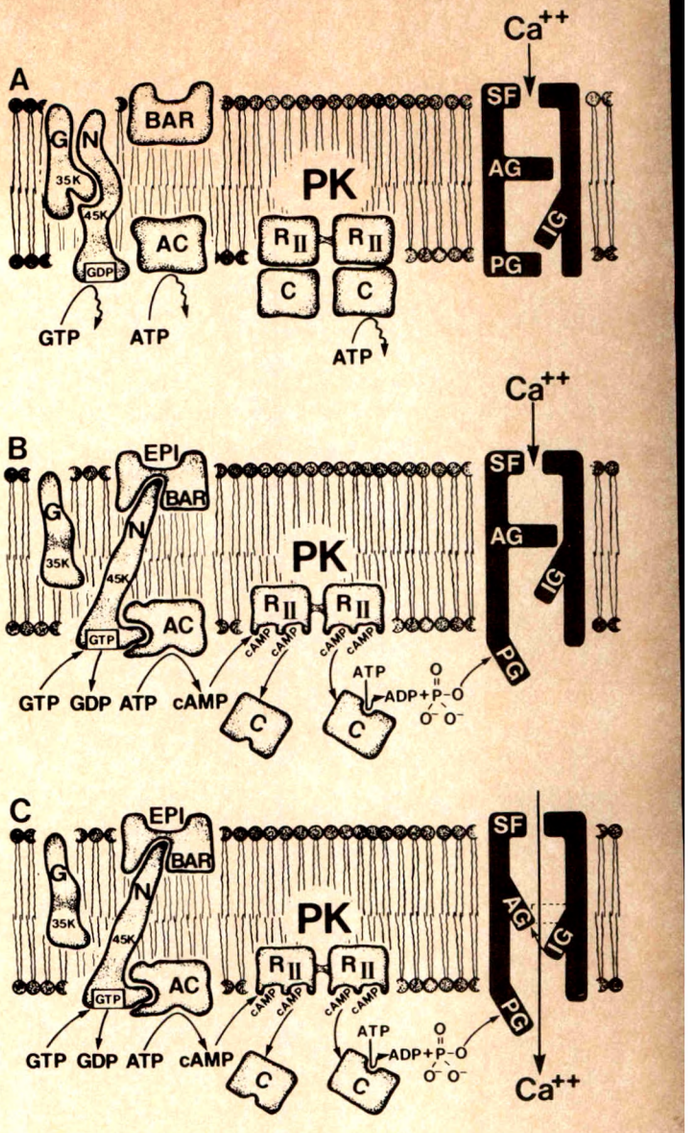

FIGURE 1. A, Hypothetical schematic representation of cardiac sarcolemmal membrane containing β-adrenergic receptor (BAR), G and N subunits of guanine nucleotide regulatory protein, adenylate cyclase (AC), regulatory (R) and catalytic (C) subunits of protein kinase (PK), and slow inward calcium channel, which has filter that is relatively selective for calcium (Ca^{++}) (SF), open inactivation (IG) gate, and closed activation (AG) and phosphorylation-regulated (PG) gates. Structures are shown at resting membrane potential in absence of β-adrenergic stimulation. **B,** binding of β-adrenergic agonist epinephrine (EPI) produces conformational change in β receptor that allows β receptor to interact with regulatory protein. This interaction causes release of GDP from N subunit. Subsequent replacement of GDP with GTP promotes dissociation of N and G subunits, stimulation of adenylate cyclase by N subunit and generation of cyclic AMP (cAMP). cAMP binds to regulatory subunits of PK and liberates catalytic subunits, which phosphorylate a component of slow channel (represented, for simplicity, by a phosphorylation-regulated "gate"). Even though β stimulation causes PG to "open," no current flows through the channel at membrane voltages below excitation threshold, due to persistent closure of activation gate. **C,** after depolarization to membrane voltages greater than threshold, activation gate opens and Ca^{++} flows down its electrochemical gradient into cell. With time, inactivation gate closes (**arrow**) and current flow ceases. On return to resting membrane potential, activation gate closes and inactivation gate reopens. For additional details regarding metabolic and electrical events depicted in this figure, see references 150 and 31, respectively.

duration after intracellular injection of cyclic GMP.[51] However, the electrophysiologic and inotropic effects of acetylcholine have been dissociated from changes in cyclic GMP concentration in several studies.[35,52]

Reduction of the slow inward current by acetylcholine may contribute to the inhibitory effects of parasympathetic stimulation on atrial muscle contractile force,[53] the spontaneous discharge rate of the sinus node[54] and AV conduction.[55] However, acetylcholine also increases outward potassium currents,[34,56] which could contribute importantly to its negative inotropic and chronotropic effects.

Role of the Slow Inward Current in the Normal Electrophysiologic Features of Cardiac Tissues

Action potentials recorded from cells in the sinus nodal region generally arise from maximum diastolic membrane potentials of −70 to −50 mV with a maximum upstroke velocity of <10 V/s[57] (Fig. 2). Action potential amplitude and amount of overshoot past zero membrane potential are less than in myocardial or Purkinje cells and are increased by elevations in $[Ca^{++}]_0$. Slow channel blockers such as manganese[58] and D-600,[59] but not tetrodotoxin,[58,60] reduce sinus nodal spontaneous discharge rate and the action potential amplitude and rate of rise. These observations suggest that the slow inward current mediates the upstroke of the sinus nodal action potential.

The slow inward current of the sinus nodal cell is reduced when $[Ca^{++}]_0$ is lowered.[59] However, even in the presence of tetrodotoxin, a decrease in $[Na^+]_0$ also reduces the slow inward current during voltage clamp and depresses the action potential upstroke,[57] suggesting that the slow inward current in sinus nodal cells may not be a pure calcium current.

Action potentials recorded from the central, or N,[61] region of the AV node also have low resting potential, action potential amplitude, overshoot and upstroke velocity (Fig. 2). They are suppressed by manganese, but not by tetrodotoxin,[62] suggesting that the slow inward current is the predominant depolarizing charge carrier. The low upstroke velocity and excitability of the AV nodal cells are presumed to be responsible for slow conduction and rate-dependent block of the node.[63] Accordingly, AV nodal conduction times and refractory periods are increased by slow channel blocking agents such as verapamil, D-600, manganese and lanthanum.[64]

The slow inward current is believed to contribute importantly to the plateau phase of action potentials recorded from atrial and ventricular myocardium and Purkinje fibers, because the slow inward current is activated at membrane potentials similar to those occurring during the plateau, whereas the fast inward sodium current is largely inactivated at these potentials (Fig. 2).[13,65] Increasing $[Ca^{++}]_0$ would be expected to increase action potential duration due to an increase in the slow inward current. However, action potential duration shortens when $[Ca^{++}]_0$ is increased and prolongs when $[Ca^{++}]_0$ is decreased.[66] In addition, some agents that enhance the slow inward current (such as isoproterenol) increase plateau height and contractile force as expected, but decrease action potential duration of Purkinje fibers. Slow-channel blockers such as D-600 and verapamil reduce the plateau-height of action potentials from myocardium and Purkinje fibers,[67–69] slightly shorten action potential duration in muscle, but prolong total Purkinje fiber action potential duration.

One explanation for this apparent paradox is that repolarizing potassium currents are increased by elevated intracellular calcium levels and are decreased when intracellular calcium levels decrease, as occurs after slow channel blockade.[70,71] A decrease in outward potassium current during blockade of the slow inward current may offset the shortening effects of reduced slow channel current on action potential duration, particularly in Purkinje fibers, and prevent significant changes in refractoriness.

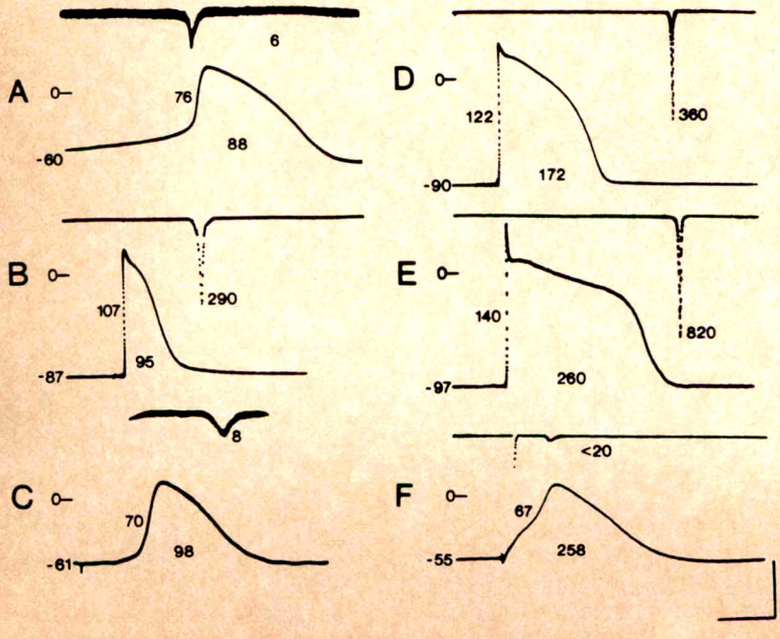

FIGURE 2. Action potentials (**lower recordings**) and dV/dt (**upper recordings**) recorded from various regions of the heart. For each panel, numbers (from **left** to **right**) indicate maximum diastolic potential, action potential amplitude, action potential duration at 90% of repolarization and dV/dt_{max}. **A,** rabbit sinoatrial node. **B,** canine atrial muscle. **C,** rabbit atrioventricular node, **D,** canine ventricular muscle. **E,** canine Purkinje fiber. **F,** diseased human ventricle. Reproduced with permission from Gilmour RF Jr, Zipes DP: Basic electrophysiology of the slow inward current. In: Antman E, Stone P, eds. *Calcium Channel Blocking Agents in the Treatment of Cardiovascular Disorders.* Mt. Kisco, NY: Futura Publishing, 1983: 1–37.

A second explanation is that catecholamines and slow channel blockers affect plateau potassium currents directly.[25,72,73] For example, norepinephrine appears to hyperpolarize cells of the canine coronary sinus[72] and shorten action potential duration of Purkinje fibers[73] by causing a specific increase in potassium permeability. In contrast, slow channel blockers such as verapamil and D-600 decrease outward potassium currents, which correlates with the ability of these drugs to slightly prolong total action potential duration in Purkinje fibers.[25] Slow channel blockers that do not affect plateau potassium current, such as nisoldipine,[74] do not prolong action potential duration.[30]

Role of the Slow Inward Current in Abnormal Electrophysiologic Features of Cardiac Tissues

Propagated action potentials can occur during experimental conditions that largely or completely inactivate the fast sodium current, such as depolarization by elevated $[K^+]_0$ or current passage, low extracellular sodium, or the presence of tetrodotoxin.[8,18,75] Agents that increase the slow inward current, such as catecholamines, histamine, phosphodiesterase inhibitors and fluoride,[43,47] facilitate induction of these slow response action potentials. Slow channel blocking agents such as verapamil,[76] manganese and D-600[77] suppress slow response activity.

Slow responses are characterized by a low upstroke velocity and excitability, slow propagation and prolonged refractoriness. Accordingly, slow responses have been implicated in the production of unidirectional block and slow conduction required for reentrant excitation under experimental conditions in vitro.[78,79] Because many of the experimental manipulations used to elicit the slow response in vitro may occur during myocardial ischemia and infarction in vivo (for example, elevated $[K^+]_0$, generalized cell depolarization, release of catecholamines[80,81]), it has been proposed that slow responses can account for slow conduction and increased refractoriness in ischemic myocardium.[75] However, slow channel blockers such as verapamil and D-600 usually decrease conduction delay and refractoriness during acute myocardial ischemia in vivo.[82] El-Sherif et al[83] have reported that these drugs increase the upstroke velocity and action potential amplitude of slowly rising action potentials recorded from subepicardial preparations isolated several days after coronary artery ligation and studied in vitro. In their study, no action potentials were suppressed by verapamil, suggesting that slow responses did not occur in these preparations. In contrast, fast sodium channel blockers such as tetrodotoxin and local anesthetic agents suppressed action potentials in the subepicardial preparations[83] and often exacerbated ischemia-induced conduction delay in vivo.[82,84]

It appears, therefore, that residual fast inward sodium current may be responsible for depressed action potentials in acutely ischemic myocardium (the so-called depressed fast response) and that the slow inward current may not play a crucial role in impulse initiation or propagation during acute myocardial ischemia. This hypothesis is supported by the observation that depression of cellular electrical activity during acute ischemia, as measured directly with microelectrodes in situ, induces action potentials that are suppressed by tetrodotoxin but not by verapamil[85] (Fig. 3).

In contrast to acutely ischemic myocardium, chronically diseased human atrium often exhibits action potentials having reduced resting membrane potentials, upstroke velocities and amplitudes that are suppressed by verapamil, but not the fast sodium channel blocker procainamide.[86,87] In addition, diseased atrium may exhibit automaticity arising from delayed afterdepolarizations that is enhanced by catecholamines and suppressed by slow channel blockers (verapamil, AHR-2666, acetylcholine), fast channel blockers (tetrodotoxin, lidocaine), and hyperpolarization secondary to increased potassium conductance (acetylcholine).[88] It appears, therefore, that although the ionic basis for abnormal electrical activity in diseased human atrium is complex, the slow inward current may play a role in impulse initiation and propagation.

Slow responses also appear to mediate some types of automaticity and action potentials in chronically diseased human ventricular myocardium.[89–92] Several

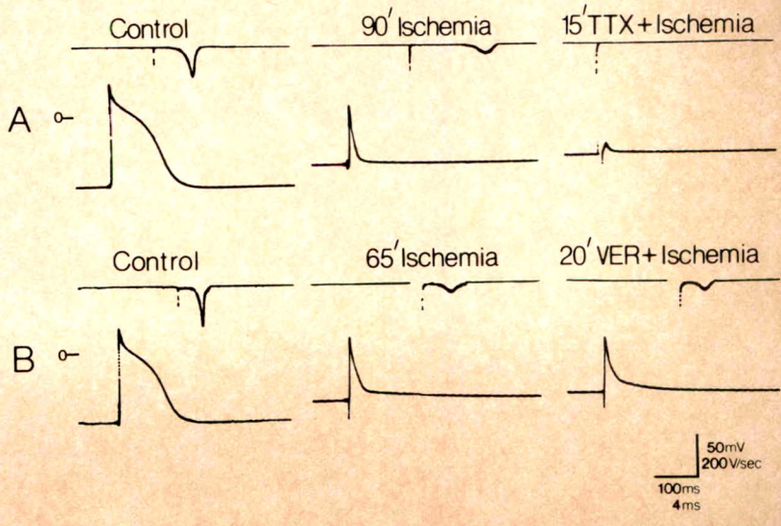

FIGURE 3. Effects of ischemia and ischemia + (TTX) **A** or + verapamil **B** on dV/dt_{max} (upper recordings) and action potential configuration (lower recordings) of atrial transplant cells. After 90 minutes of ischemia, transplant cell **A**, was exposed to TTX (10^{-5} M) for 15 minutes. TTX progressively decreased action potential amplitude and dV/dt_{max} and cell became inexcitable. After 65 minutes of ischemia in another atrial transplant **B**, action potential configuration was similar to that seen at 90 minutes of ischemia in A. Exposure of this cell to verapamil (2×10^{-6} M) for 20 minutes did not produce inexcitability. Reproduced with permission from *Circ Res*.[85]

investigators have recorded action potentials with slowly rising upstrokes and prolonged refractoriness that are suppressed by verapamil and D-600, but not by tetrodotoxin. The resting potential, action potential amplitude and upstroke velocity of these cells are increased by elevated $[Ca^{++}]_0$ and decreased by low $[Ca^{++}]_0$.[91] However, tetrodotoxin and lidocaine reduce the amplitude of some depressed action potentials, suggesting that partially inactivated fast sodium channels may still be capable of initiating action potential upstrokes in some cells.[89,92]

Various forms of abnormal automaticity have been described in diseased human ventricle. Several forms arise from delayed afterdepolarizations or from levels of membrane potential at which the fast inward sodium current is normally inactivated.[89,90] These types of automaticity generally are enhanced by catecholamines, suppressed by verapamil and only occasionally suppressed by tetrodotoxin.[89,90]

Triggered activity arising from delayed afterdepolarizations (also called oscillatory afterpotentials[93]) has also been produced experimentally, most notably by exposure to toxic concentrations of cardiac glycosides,[93,94] and by interventions that favor increased calcium uptake, such as superfusion with solutions containing catecholamines, elevated $[Ca^{++}]_0$ and reduced $[K^+]_0$.[75,95,96] In contrast to most forms of automaticity, triggered activity is accelerated, rather than suppressed, after overdrive pacing. Triggered sustained rhythmic activity occurs in apparently normal atrial myocardium,[85,88] upper pectinate muscles bordering the crista terminalis[97] and mitral valve fibers[98,99] as well as in diseased atrium[88] and ventricle.[89,90,100] Low $[Ca^{++}]_0$ (and, therefore, low $[Ca^{++}]i$) or slow channel blockade with verapamil, AHR-2666 and manganese[93,94,98] suppress delayed afterdepolarizations. Therefore, the slow inward current may modulate the amplitude of delayed afterdepolarizations, despite the fact that the afterdepolarizations can occur at membrane potentials 30 to 50 mV negative to the threshold voltage for the slow inward current. Recent evidence indicates that calcium entry through the slow inward current contributes to oscillatory release of calcium from intracellular stores and a subsequent change in membrane conductance. This permits flow of a small depolarizing current, probably carried by sodium.[96,101] Voltage clamp studies suggest that the oscillatory transient inward current responsible for delayed afterdepolarizations may be a physiologic component of cardiac cellular electrical activity, becoming more prominent when intracellular calcium levels are increased.[101] Induction of the transient inward current also may be facilitated by an increase in $[Na^+]i$, such as occurs after inhibition of the sodium-potassium pump, because increased $[Na^+]i$ increases $[Ca^{++}]i$ through a sodium/calcium exchange.[102,103]

Induction of the transient inward current after increase of [Na]i and $[Ca^{++}]i$ may explain the sensitivity of delayed afterdepolarizations to changes in calcium flux, as well as their depression by decreases in $[Na^+]_0$[104] and exposure to tetrodotoxin[94,99] and lidocaine.[94,105] Spontaneously occurring or epinephrine-induced delayed afterdepolarizations in human atrium are not suppressed by tetrodotoxin or lidocaine, however, raising the possibility that mechanisms for triggered activity under various circumstances may differ.[88]

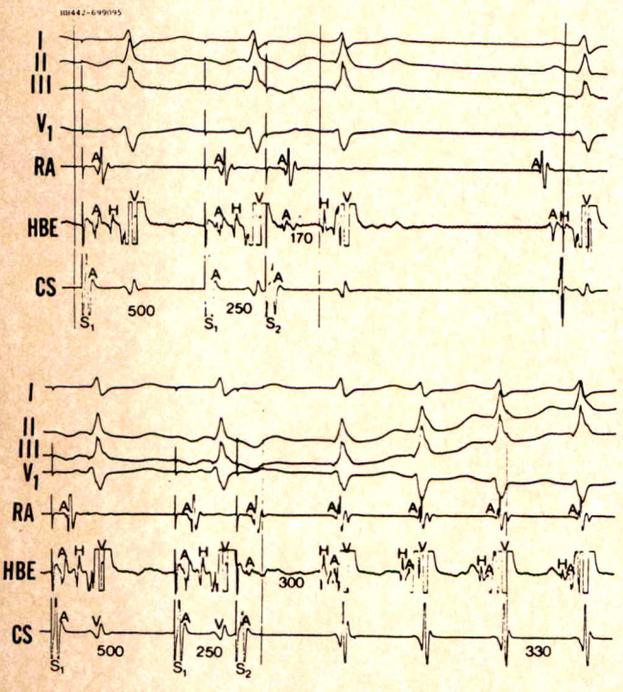

FIGURE 4. Initiation of supraventricular tachycardia in patient with dual atrioventricular (AV) nodal pathways. The panels show last 2 paced beats (S_1) of train delivered to coronary sinus at pacing cycle length of 500 ms. Results of premature atrial stimulation at an S_1-S_2 interval of 250 ms on 2 occasions are shown. In **top panel,** S_2 was conducted to ventricle with an AH interval of 170 ms. In the **bottom panel,** S_2 was conducted with an AH interval of 300 ms, followed by AV nodal reentry. CS = coronary sinus electrogram; HBE = His bundle electrogram; RA = right atrial electrogram; I, II, III, V_1 = scalar electrocardiographic leads. Reproduced with permission from *Circulation.*[109]

The Slow Inward Current and Cardiac Arrhythmias: Supraventricular Tachycardias, Atrioventricular Nodal Supraventricular Tachycardias

The weight of evidence implicates reentry as the mechanism responsible for initiation and maintenance of AV nodal supraventricular tachycardias (SVTs) and places the site of the anterogradely conducting pathways in the AV node where conduction is slow channel-dependent. The site of the retrogradely conducting pathway, as well as the geometry and electrophysiologic features of its fibers, are still being defined and may not be the same for all patients with AV nodal reentrant SVT (Fig. 4).

Verapamil or diltiazem, administered intravenously, has been shown to terminate effectively episodes of AV nodal reentrant SVT in patients.[106–112] Slow channel blockers administered orally may produce similar results. Generally, the slow channel blockers terminate AV nodal reentrant SVTs by causing prolongation and eventual block of anterograde AV nodal conduction.[109] This may be analogous to experiments in an isolated rabbit AV nodal preparation in which verapamil prevented AV nodal reentry and initiation of atrial tachy-

cardia by causing premature atrial impulses to block rather than to conduct with the delay needed to initiate reentry.[113] Verapamil primarily (but not exclusively[114]) affects conduction and refractoriness in the anterogradely conducting pathway, exerting no significant effect on the pathway used for retrograde conduction during the SVT[112] (Fig. 5 and 6). This observation lends further credence to the concept that, at least in some patients with AV nodal reentrant SVT, the retrogradely conducting pathway may not be composed of typical AV nodal fibers.[115,116]

Supraventricular Tachycardia Related to Wolff-Parkinson-White Syndrome

Reciprocating tachycardia in the Wolff-Parkinson-White (WPW) syndrome most often involves conduction over the AV node anterogradely, and thus involves slow channel–dependent fibers in this portion of the reentrant loop.[117] The remaining fibers in the reentrant pathway, atrium, ventricle or accessory pathway are normally fast channel–dependent.

Verapamil exerts no significant direct electrophysiologic effects on the accessory pathway (Fig. 7) and terminates SVT in patients with WPW syndrome by slowing and blocking conduction over the normal AV node.[109,112] Thus, after verapamil administration, reciprocating tachycardia in the WPW syndrome most often terminates during anterograde[118] conduction due to AV nodal block. If verapamil does not produce block in the AV node during SVT, the tachycardia continues at a slower rate, resulting from prolongation of AV nodal conduction time. Verapamil may actually produce faster ventricular rates during atrial fibrillation in patients with WPW syndrome, probably due to reflex sympathetic stimulation in response to peripheral vasodilation and transient hypotension, shortening the refractory period of the accessory pathway.[109,119] Verapamil has been incriminated in precipitating ventricular fibrillation after administration to a patient with atrial fibrillation.[120] Intravenous verapamil should not be given to patients who have WPW syndrome and atrial fibrillation. Oral verapamil does not appear to generate the same risk of increased ventricular rate during atrial fibrillation and probably could be used if indicated.

Some data suggest that the AV node in patients with WPW syndrome may conduct more rapidly and exhibit a shorter refractory period than in patients with SVT unrelated to the WPW syndrome.[121] Verapamil appears

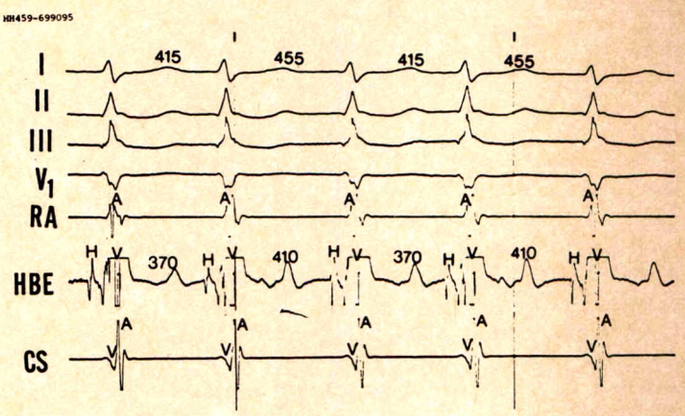

FIGURE 5. Same patient as in Figure 4. After intravenous verapamil administration, supraventricular tachycardia developed cycle length alternans of 40 ms, caused by alteration in AH intervals. The HA interval, HV interval and atrial activation sequence remain constant. Reproduced with permission from *Circulation.*[109] Abbreviations as in Figure 4.

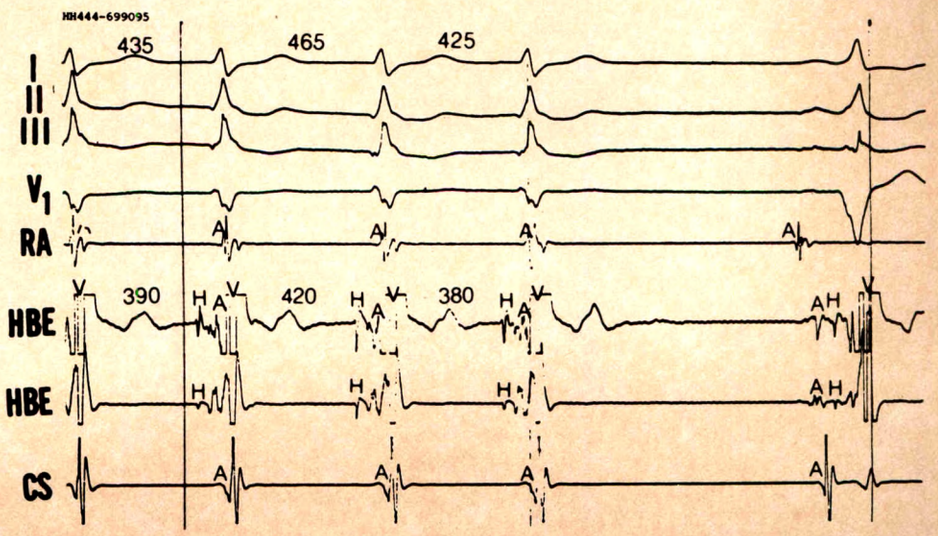

FIGURE 6. Same patient as in Figures 4 and 5. Supraventricular tachycardia terminated because of block of atrial depolarization proximal to His bundle recording site. Reproduced with permission from *Circulation.*[109] Abbreviations as in Figure 4.

to prolong the AV nodal conduction time and the functional and effective refractory periods of the AV node to a lesser extent in patients with WPW who have SVT, than in patients who have SVT due to AV nodal reentry.[109] The reason for the reduced electrophysiologic response of the AV node to verapamil in patients with WPW syndrome is unknown.

Sinus Nodal Reentry

Premature stimulation can produce slow propagation in the sinus node, block in some areas, and the development of repetitive responses, most likely owing to reentry. Evidence from a number of studies in man[122–124] and animals[125,126] supports the concept that sustained reentry in the sinus node can occur and cause SVT. Recently, Allessie and Bonke[125] showed that the reentrant circuit in the isolated rabbit preparation was located entirely within the sinus node and that the atrium was not an essential link. This observation suggests that slow channel–dependent tissue may comprise the critical portion of the reentrant circuit.

SVTs thought to be due to sinus nodal reentry generally have a slower rate than SVTs due to AV nodal reentry or reentry over an accessory pathway, although significant overlap exists. P waves appear in front of the QRS complex and exhibit a contour similar to the P wave during sinus rhythm, with the expected sequence of activation beginning in the upper right atrium and progressing caudally (Fig. 8).

The effects of verapamil in patients with SVT from sinus nodal reentry have not been investigated systematically. Verapamil given intravenously to dogs appeared to exert a differential response on the sinus and AV nodes.[127] Verapamil prolonged AV nodal conduction time and produced AV block at plasma concentrations that did not significantly alter the spontaneous discharge rate of the sinus node. Verapamil's effect on conduction within the sinus and AV nodes was not compared. Similar observations have been made in man.[128] When given after β-adrenergic blockade, verapamil achieves more significant depression of sinus nodal automaticity. It is possible that a reflex increase in sympathetic tone prevents verapamil, when given alone intravenously, from significantly altering sinus nodal automaticity.[129]

Curry and Krikler[122] found that verapamil promptly terminated SVT due to sinus nodal reentry in 2 patients and prevented reinitiation of the tachycardia in 5. We have given verapamil to 2 patients with SVT caused by AV nodal reentry and sinus nodal reentry.[109] In both patients, the SVT caused by sinus nodal reentry persisted several minutes after verapamil had terminated the AV nodal reentrant SVT. It would appear that the sinus nodal reentrant SVT resisted the suppressing effects of verapamil more than did the AV nodal reentrant SVT. In fact, in the second patient, verapamil may have even caused the sinus nodal reentrant SVT, which could not be produced before verapamil administration, by initiating partial conduction delay in the sinus node.

Atrial Reentry

Reentry within the atrium, unrelated to the sinus node, has been shown experimentally to occur in the rabbit[130] and dog[131] atrium, with or without an anatomic obstacle, and may be a cause of SVT in man. Examples of SVT purported to be due to atrial reentry have been cited,[124,132,133] but their relative infrequency in published reports suggests it is not a common cause of SVT in man. Atrial reentry differs from sinus nodal reentry by a P-wave morphology and atrial sequence of activation unlike that found during sinus rhythm. Distinguishing atrial tachycardia owing to automaticity from atrial tachycardia sustained by reentry over very small areas (micro-reentry) is very difficult; therefore, conclusions regarding electrophysiologic mechanisms of this SVT based on presently available information must be accepted cautiously.

It can be speculated that verapamil might terminate SVT if it were due to reentry over diseased atrial fibers that were slow channel–dependent. To our knowledge,

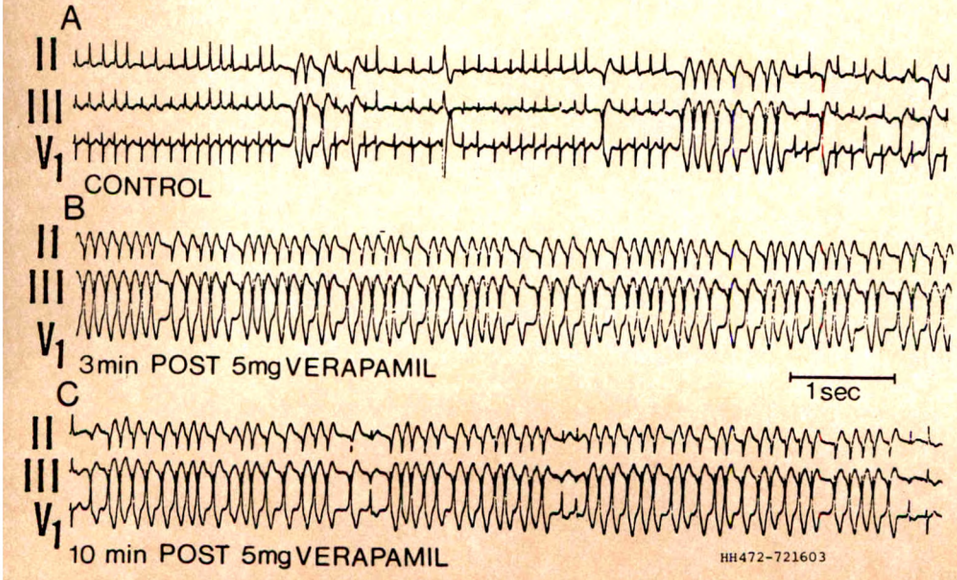

FIGURE 7. Effect of verapamil on ventricular activation during atrial fibrillation in patient with Wolff-Parkinson-White syndrome. Tracings were recorded before and 3 and 10 minutes after verapamil administration. Increase in ventricular rate and increased number of preexcited ventricular complexes occurred 3 minutes after verapamil administration. Effect diminished at 10 minutes. Reproduced with permission from *Circulation*.[109]

however, no information exists regarding the clinical effects of verapamil on SVT caused by atrial reentry. In experimentally induced reentrant atrial tachycardia in the rabbit, verapamil exerted no significant effects.[134]

In man, SVTs characterized as automatic by a variety of criteria have been described,[133,135–137] but most of these are incomplete. Their differentiation from other forms of SVT, such as sinus nodal reentry (if the P wave of the automatic atrial tachycardia resembles the sinus-initiated P wave) or atrial reentry (particularly if caused by micro-reentry), may be difficult. However, in view of the experimental findings of triggered activity from a variety of atrial fibers, including human mitral valve, it is possible that such triggered activity occurs in man. Triggered activity has been demonstrated in isolated preparations of the mitral valve, coronary sinus and normal and diseased atria. Suppression of such activity by verapamil suggests but does not prove that the slow inward current may play a role in the genesis of this triggered activity. At present, however, the meager clinical information does not support the conclusion that such verapamil-suppressed triggered activity is responsible for many clinically occurring atrial tachycardias.

We have performed electrophysiologic studies on several patients who had SVT that met previously established criteria for automaticity.[109] The responses of automaticity in these patients to various pacing protocols were not characteristic of triggered activity. Verapamil resulted in a decrease in the ventricular response to the atrial tachycardia without suppression of the tachycardia (Fig. 9).

Nonparoxysmal Atrioventricular Junctional Tachycardia

Nonparoxysmal AV junctional tachycardia is often due to cardiac surgery, acute rheumatic heart disease, digitalis intoxication or myocardial infarction.[138] Sometimes no origin can be discovered and the patient may be otherwise healthy. Conversely, nonparoxysmal AV junctional tachycardia at very rapid rates has been described in 4 children, and was found to be a very serious, difficult-to-control SVT.[139] The mechanism responsible for nonparoxysmal AV junctional tachycardia is generally assumed to be enhanced automaticity for the His bundle or a contiguous structure that possesses automatic activity. In some instances, it is possible that nonparoxysmal AV junctional tachycardia originates in small groups of atrial fibers that have a mass insufficient to generate a P wave that can be recorded on a scalar ECG. In such instances, careful mapping during an invasive electrophysiologic study is necessary to find the area of atrial depolarization.[140] Wenckebach periods may occur, but the presence of exit block has not yet been demonstrated clinically, and the block may be in the AV node, with the origin of the nonparoxysmal AV junctional tachycardia proximal to the site of His bundle recording. In an interesting study of accelerated junctional escape beats, shorter junctional escape intervals were observed after premature atrial complexes, thus raising the possibility of overdrive acceleration in these fibers. Pacing studies and the effects of verapamil were not tested.[141]

Clinical information regarding the effects of slow channel blockers on nonparoxysmal AV junctional tachycardia is negligible. Automaticity in the His bundle is generally thought to be similar to that found in Purkinje fibers and therefore not slow channel-dependent. However, it is certainly possible that some of the interventions responsible for nonparoxysmal AV junctional tachycardia may create conditions in which the slow inward current is operative.

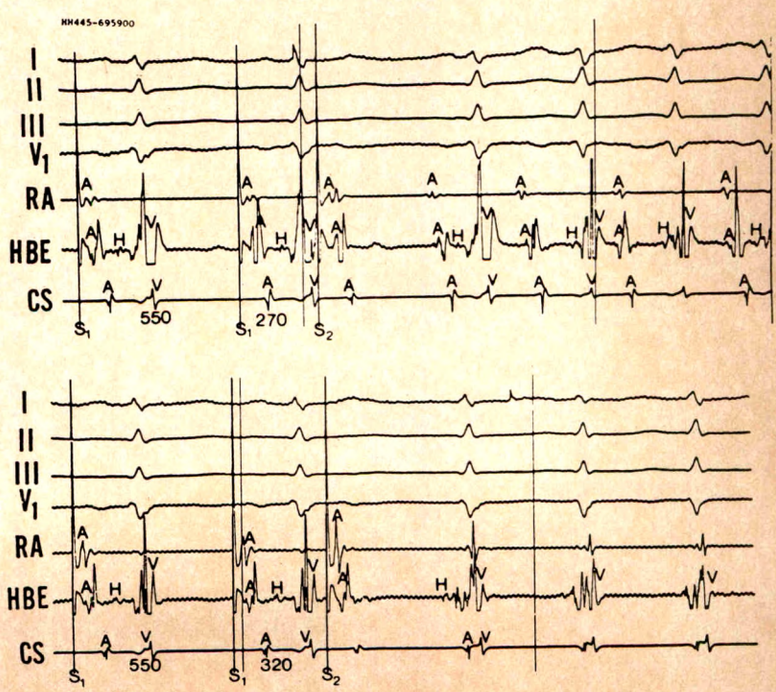

FIGURE 8. Initiation of atrioventricular (AV) nodal and sinus nodal reentrant tachycardias. In **top panel,** premature stimulation of high right atrium at S_1-S_2 interval of 270 ms initiated atrial tachycardia with activation sequence similar to that occurring during high right atrial pacing. In **bottom panel,** premature stimulation of right atrium at S_1-S_2 interval of 320 ms resulted in prolonged AH interval and initiated AV nodal reentry. Retrograde low right atrial activation occurred before ventricular activation and was followed by left (coronary sinus) and high right atrial activation. Reproduced with permission from *Circulation.*[109]

Atrial Flutter and Atrial Fibrillation

Whether reentry or automaticity or both is responsible for atrial fibrillation is still unknown.[142] Much evidence supports the role of reentry as a cause of atrial flutter,[143] but abnormal automaticity cannot be excluded.[131] Because sustained atrial flutter or atrial fibrillation occurs infrequently in patients without heart disease, it is possible that the atria in these patients manifest abnormal electrophysiologic characteristics, some of which may be consistent with slow channel–dependent action potentials.[88] At present, however, insufficient data prevent any definite conclusions.

Verapamil reportedly converts approximately 30% of episodes of atrial flutter and 16% of episodes of atrial fibrillation to sinus rhythm.[144] Based on our own studies, we think these data may be optimistic. The consistent effect of verapamil in patients with atrial flutter or atrial fibrillation (without WPW syndrome) is a prompt decrease in the ventricular response, lasting at least 30 minutes[109] (Fig. 10).

In some patients with atrial flutter or atrial fibrillation, the slow response may play a role in the genesis and maintenance of the arrhythmias. However, this con-

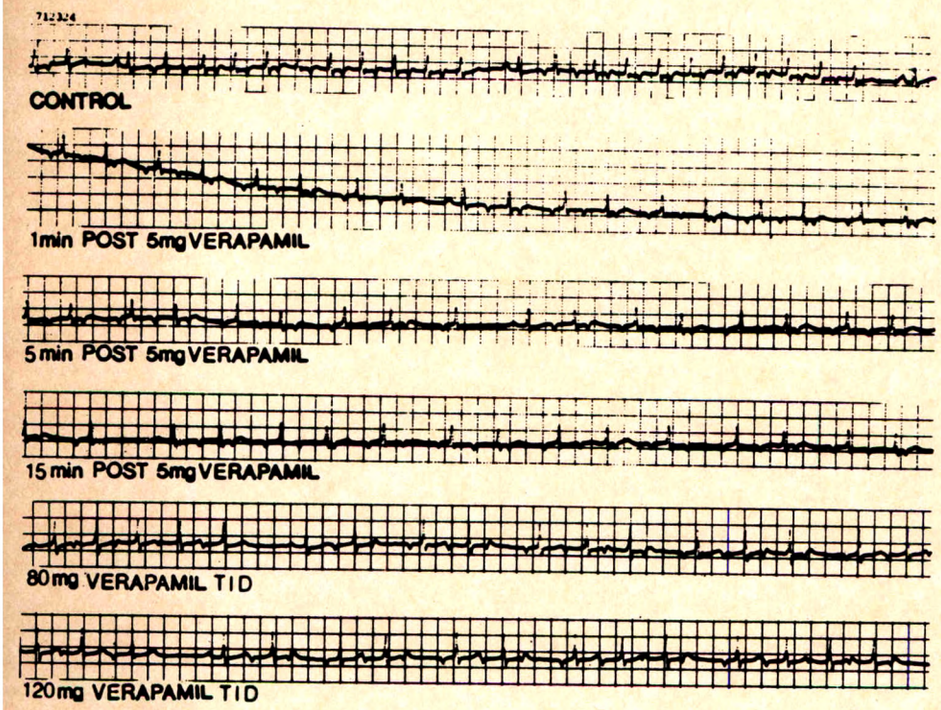

FIGURE 9. Effects of intravenous and oral verapamil in patient with ectopic (presumed automatic) atrial tachycardia. Note that verapamil produced slight slowing of discharge rate of atrial tachycardia and primarily caused reduction in ventricular response. Reproduced with permission from Zipes DP, Gilmour RF Jr. Calcium antagonists and their potential role in the prevention of sudden coronary death. In: Greenberg, HM, Dwyer EM Jr, eds. Sudden Death. Ann N Y Acad Sci 1982;382:258–288.

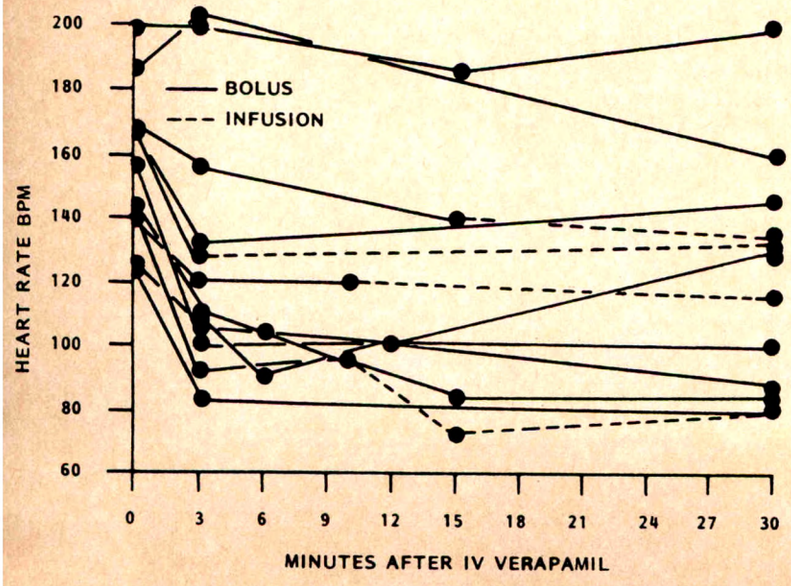

FIGURE 10. Response of atrial fibrillation after intravenous verapamil administration. Heart rate in beats per minute (BPM) is plotted against time in minutes after intravenous administration of verapamil. **Solid lines** indicate response after bolus injection and **dashes** indicate intravenous infusion. Mean ventricular response was reduced to 81.6% of control rate at 3 minutes ($p < 0.01$). After maximal response, ventricular rate tended to increase slightly. Reproduced with permission from *Circulation*.[109]

clusion is based on consideration of in vitro observations of transmembrane potentials recorded from diseased human atrial fibers.[88] No clinical information is available to support the importance of the slow inward current in these SVTs.

Ventricular Tachycardia

Although it is quite clear from experimental studies that the slow response can be created and demonstrated in a variety of preparations of ventricular fibers, it is not at all clear whether the slow response can be related causally to the genesis of ventricular tachycardia in man. Only a few noncontrolled studies of the response of ventricular tachycardia to slow channel blockers have been reported in a small number of patients, and the data are inconclusive.[111,145] Generally, verapamil has not been very effective in terminating ventricular tachycardia, although exceptions have been reported.[146–148] In 1 report, the mechanism of ventricular tachycardia may have been triggered activity.[149] Thus, preliminary data suggest that the slow response may not be important in the genesis of most ventricular tachycardias and that the slow channel blockers may not be as effective in treating ventricular tachycardia as they are in treating SVT.

In summary, observations from experimental and clinical studies suggest that slow channel blocking agents may suppress arrhythmias requiring slow channel–dependent tissues for their initiation or perpetuation. Most often, these arrhythmias include sinus and AV nodal reentrant tachyarrhythmias and reciprocating tachycardia in the WPW syndrome when 1 of the pathways involves the AV node. Damaged atrial and ventricular tissue also may generate slow response–mediated automaticity, triggered activity and reentry under certain circumstances. The clinical importance of triggered activity remains to be established. The contribution of slow responses to arrhythmia development in vivo is uncertain, however, because the available experimental and clinical data indicate that many supraventricular and ventricular arrhythmias are not suppressed by slow channel blockers. Although preliminary reports suggest that such agents as verapamil or diltiazem do not appear to be particularly effective for the treatment of ventricular tachycardia, they do have diverse actions on autonomic receptors, vascular tone and myocardial metabolism that could make them useful for the prevention of sudden death. This and many other potential actions of this novel class of drugs remain to be investigated.

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Calcium-Entry Blocking Agents in the Treatment of Systemic Hypertension

BRIAN F. ROBINSON, MD

Calcium-entry blocking agents resemble established dilators such as diazoxide, minoxidil and hydralazine in that they act predominantly on the arterial resistance vessels and have little or no effect upon the veins. They have therefore been evaluated in the treatment of hypertension. Controlled studies have shown that verapamil and nifedipine are effective in decreasing blood pressure when given as sole agents. The antihypertensive effect of nifedipine is additive with that of a β blocker, and nifedipine is also effective when given as a "third step" agent in combination with a β blocker (or α methyldopa) and a diuretic. In contrast to other directly acting dilators, nifedipine causes, at most, only moderate stimulation of renin secretion and verapamil does not increase renin release at all; neither drug induces sodium retention. Both verapamil and nifedipine produce a moderate incidence of unwanted effects; these are mostly subjective in nature, but verapamil may cause constipation that is occasionally severe and nifedipine sometimes causes ankle swelling. Calcium-entry blockers should be considered as initial therapy when some contraindication exists to the use of other standard drugs. Nifedipine appears preferable to hydralazine for use in combination with a β blocker and a diuretic: it is at least as effective as hydralazine and has a lower incidence of serious adverse effects.

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The peripheral dilators such as hydralazine and diazoxide that have proved effective in the treatment of hypertension differ widely in their chemistry and basic mechanism of action, but they all share 1 common characteristic: they act predominantly upon arteriolar resistance vessels and have little or no effect on veins.[1] The observation that calcium-entry blocking agents such as verapamil[2] and nifedipine[3] also act selectively on the resistance vessels suggested that they too might be particularly suited to the treatment of hypertension. It was therefore decided to evaluate the effectiveness of these drugs in patients attending the hypertension clinic of this hospital; over the past 5 years more than 100 men and women have been treated as outpatients with nifedipine and, more recently, verapamil. It is against this background that the effectiveness of the calcium-entry blocking agents will be evaluated and an attempt made to assess their likely role in the treatment of hypertension.

After early uncontrolled observations on the blood pressure-decreasing effect of verapamil, its antihypertensive action was subsequently confirmed in controlled trials,[4,5] and the antihypertensive action of nifedipine was also demonstrated.[6] In recent years, the effectiveness of the calcium-entry blocking agents in the treatment of hypertension has been systematically investigated and it has become clear that drugs of this class are able to induce a sustained decrease in arterial pressure, both when given alone and also when given in combination with other standard agents.

From the Department of Medicine, St. George's Hospital Medical School, London, England.

Address for reprints: Brian F. Robinson, MD, FRCP, Department of Pharmacology, St. George's Hospital Medical School, London SW17 ORE, England.

Effectiveness of Calcium-Entry Blocking Drugs as Antihypertensive Agents

Use as sole therapy: The antihypertensive action of both verapamil and nifedipine has been assessed in studies using continuous 24-hour intraarterial blood pressure recording. In 16 patients studied in this way, verapamil, in a dosage of 120 to 160 mg 3 times daily decreased average daytime pressure from 180/95 to 158/79 mm Hg ($p < 0.001$); heart rate decreased significantly by about 10 beats/min.[7] In a similar study by the same investigators, nifedipine slow-release tablets given twice daily in a total daily dose of 40 to 120 mg decreased supine arterial pressure in 17 patients from an average of 175/98 to 141/80 mm Hg ($p < 0.001$) and approximately the same decrease in pressure was maintained throughout the 24 hours; heart rate was not significantly

changed.[8] A study by another group in which nifedipine capsules were given in a dosage of 10 to 20 mg 3 times daily yielded similar results.[9] In all 3 studies the normal circadian rhythm of arterial pressure, with a decrease in the night hours and a relatively rapid increase in the early part of the morning, was maintained during drug therapy.

When taken in capsule formulation, nifedipine is rapidly absorbed, and absorption is even more rapid if the capsule is bitten into and the contents are retained beneath the tongue. The drug has therefore been used in those uncommon circumstances when patients present with severe hypertension and rapid decrease in pressure appears indicated. In a study of 17 patients with severe primary hypertension who were not receiving any other therapy, the short-term effects of 10 mg of nifedipine were measured by full hemodynamic monitoring.[10] Maximal circulatory effect was achieved within about 30 minutes of oral administration to the fasting subjects and within 15 to 20 minutes of sublingual dosage. The maximal decrease in mean arterial pressure averaged 36 mm Hg (−24%); heart rate increased by 22% and cardiac output by 31% ($p < 0.01$). In 3 patients with hypertensive encephalopathy and acute left ventricular failure, arterial pressure decreased from an average of 307/164 to 237/115 mm Hg within 15 minutes; another 10 mg of nifedipine was given after 1 hour and blood pressure decreased progressively to an average of 176/89 mm Hg over the next hour.

In a recent study of 10 patients who presented with "hypertensive crisis" and impaired renal function, nifedipine, 10 to 20 mg sublingually, decreased arterial pressure within 1 hour from 211/134 to 172/107 mm Hg ($p < 0.001$); heart rate increased from 83 to 98 beats/min.[11] In the 7 patients who had evidence of encephalopathy, the signs of this complication subsided. Verapamil is absorbed more slowly than nifedipine and must therefore be given parenterally if rapid action is required; 5 to 10 mg given slowly intravenously was reported to be consistently effective in decreasing arterial pressure when it is acutely increased.[12]

Use in Combination With a Beta-Adrenoceptor Antagonist or Alpha Methyldopa

The depressant effect of verapamil on the atrioventricular node may lead to the development of heart block or other serious rhythm disturbance if it is given intravenously to patients who have already received a β-adrenoceptor antagonist. The risk of such adverse effects is small with oral administration, but it is not negligible,[13] and the possibility of this interaction has deterred physicians from using the combination in the treatment of hypertension. Nifedipine has no significant effect upon the conducting system and can safely be given with a β blocker. The antihypertensive effects of the 2 types of drugs have been shown to be clearly additive. In a single-blind study of 12 hypertensive men, metoprolol (100 mg twice daily) and nifedipine (10 mg 3 times daily) were given either alone or in combination. Supine arterial pressure averaged 178/99 mg Hg with placebo, 158/88 mm Hg with nifedipine, 156/92 mm Hg with metoprolol and 141/84 mm Hg with the combination of the 2.[14] The decrease in pressure induced by the 2 drugs separately and the additional decrease that resulted when nifedipine was added to metoprolol were significant ($p < 0.05$). In an open trial involving 17 patients, similar results were obtained with the combination of propranolol and nifedipine.[15]

Nifedipine has also been used in combination with α methyldopa; in a placebo-controlled trial, the 2 drugs were shown to have additive effects in decreasing arterial pressure.[16]

Calcium-Entry Blocking Agents Combined With Diuretics

It is not yet clear to what extent calcium-entry blockers can usefully be combined with diuretics. In several studies using verapamil, thiazide diuretics were given concurrently,[5,17] but there has been no systematic investigation of the extent to which the antihypertensive effects of the 2 classes of drugs may be additive. Clinical experience suggests that, in some patients at least, a diuretic can cause a further decrease in pressure when added to verapamil and also when added to the combination of nifedipine and a β blocker.

Calcium-Entry Blockers as Third Step Agents

Nifedipine is frequently effective when added to the combination of a β blocker and a diuretic. In a double-blind, placebo-controlled trial carried out in this department, we examined the effect of adding nifedipine (30 to 60 mg daily in divided doses) to the combination of a β blocker and a diuretic. Arterial pressure decreased significantly by 19/11 mm Hg supine ($p < 0.025$) and 21/12 mm Hg standing ($p < 0.05$); heart rate and body weight showed no significant change.[18] In a similar study in which nifedipine at 3 dose levels (30, 60 and 90 mg/day) was added to atenolol (100 mg/day) and bendrofluazide (5 mg/day), a dose-dependent decrease in arterial pressure was observed; the maximum reduction was 23/16 mm Hg supine and 24/19 mm Hg standing ($p < 0.001$).[19] In an open study of 20 patients in whom hypertension was inadequately controlled by the combination of a β blocker, diuretic and vasodilator (mainly hydralazine), the substitution of nifedipine for the vasodilator resulted in a decrease in arterial pressure averaging 25/11 mm Hg supine; the results of this open trial were not analyzed statistically.[20]

The effectiveness of nifedipine when added to the combination of a β blocker and diuretic is thus well established, and the decrease in blood pressure that is achieved appears broadly comparable to that reported with hydralazine.[21] Some patients who are resistant to hydralazine respond well to nifedipine[18,20]; the reverse may also be true, but has not yet appeared in a published report.

Mechanism of Action of Calcium-Entry Blocking Agents in Hypertension

As with other dilator agents, verapamil and nifedipine decrease arterial pressure by relaxing the vascular smooth muscle of the arterioles and so decreasing peripheral resistance. The forearm resistance vessels of patients with primary hypertension are, however, more

sensitive to the dilator action of verapamil than those of normal subjects.[22,23] The enhanced responsiveness to verapamil is believed to reflect increased activity of the potential-operated calcium channels. It has been postulated that this abnormality is a basic functional disorder underlying the increased peripheral resistance.[24] It may therefore be that calcium-entry blocking agents decrease peripheral resistance by specifically reversing the functional abnormality that is maintaining the hypertensive state. If this were so, drugs of this class should be more effective in decreasing blood pressure in patients with hypertension than in normal subjects. This has been claimed for short-term administration of nifedipine,[25,26] but the same may be true of some other antihypertensive agents. If calcium-entry blockers act by specifically reversing pathologically augmented tone, then they should also restore a more physiologic balance of resistances in different beds than would be the case with nonspecific dilators. There is, as yet, no evidence for or against this view.

Effect on Plasma Renin Activity and Sodium Excretion

Short-term administration of nifedipine leads to an increase in plasma renin activity.[27] During long-term administration, nifedipine may induce an increase in renin secretion in some patients, but on average, plasma renin activity has either been unchanged[9] or has shown a statistically insignificant increase.[14,28] Verapamil causes no increase in plasma renin activity during either short-[29] or long-term therapy.[17,29] These effects contrast with those of dilators such as diazoxide and hydralazine, which consistently induce substantial increases in plasma renin activity.[30,31]

In striking contrast to diazoxide, minoxidil and, to a lesser extent, hydralazine, the calcium-entry blockers do not give rise to sodium retention.[7–9] This may be partly accounted for by the lack of effect on the renin-angiotensin-aldosterone system, but it may also be that they have differing direct effects on the kidney.

Unwanted Effects

The depressant action of verapamil on the cardiac conducting system rarely causes any problem in the treatment of hypertension. Occasionally, the antiarrhythmic properties of the drug may prove an advantage in a patient who has both hypertension and a history of supraventricular tachyarrhythmias.

The major adverse effect reported by patients treated with verapamil is constipation, and this may occasionally necessitate withdrawal of the drug.[32] A small proportion of patients complain of flushing or headache.

Nifedipine appears more likely to provoke symptoms of flushing, headache or burning in the legs; symptoms most often occur a short time after taking the drug and are less of a problem with the sustained release preparation, which causes significantly lower peak concentrations. Nifedipine may infrequently provoke anginal pain at rest in patients with preexisting, but perhaps unrecognized, coronary artery disease.[18,33] The mechanism is uncertain, but the induction of a coronary "steal" phenomenon seems the most likely cause. A not uncommon and occasionally irksome effect of nifedipine is development of ankle edema, which is sometimes quite severe. It typically occurs in the absence of other signs of cardiac failure (1 such patient in our clinic was able to play water polo!) and does not result from primary retention of sodium by the kidney because it is resistant to conventional doses of diuretics.[16] It is widely believed that ankle edema results from a selective dilatation of the precapillary resistance vessels leading to increased capillary pressure, but proof of this hypothesis is lacking.

Neither verapamil nor nifedipine appears to carry the risk of serious immunologic adverse effects such as the drug-induced lupus syndrome that is occasionally seen with hydralazine. Verapamil has no effect on serum lipids.[32]

Clinical Use of Calcium-Entry Blocking Agents in Treatment of Hypertension

Verapamil and nifedipine are both suitable for the initial treatment of patients with mild to moderate hypertension. They offer an alternative to β-adrenoceptor antagonists for patients in whom that group of drugs is contraindicated by coexisting asthma or peripheral vascular disease. A calcium-entry blocker can also be considered for patients in whom a thiazide diuretic might normally be used but is contraindicated by a predisposition to diabetes mellitus, gout or hypokalemia. In theory, verapamil is preferable to nifedipine for use as a sole drug in view of its tendency to slow rather than speed the heart rate; in practice, there seems to be little difference between the 2 agents. It is not yet clear which groups of patients can be expected to respond best to a calcium-entry blocker, but it has been suggested that, in contrast to β-adrenoceptor blockers, it generally is the patients who are older or have suppression of plasma renin activity who have the greatest decrease in pressure.[34] Both verapamil and nifedipine must be given at least twice daily in contrast to the once daily therapy that is available with both β blockers and diuretics. This is a disadvantage.

If a second drug needs to be added to the calcium-entry blocker, it will normally be a diuretic if verapamil has been used. The extent to which the hypotensive actions of the 2 classes of drugs are additive has, however, not yet been defined. If nifedipine has been used initially, it appears logical to add a β blocker as the next step because the effectiveness of this combination is well documented. It is worth noting that nifedipine can often be successfully substituted for the diuretic in patients whose condition was previously controlled by a β-blocker/thiazide combination and in whom withdrawal of the thiazide is necessitated by adverse metabolic effects.

The major established indication for the use of nifedipine is as a third step agent in combination with a β blocker (or α methyldopa) and a diuretic. Nifedipine is clearly preferred to hydralazine in this situation. It is at least as effective in decreasing arterial pressure, probably has a lower incidence of subjective adverse

effects and, most importantly, does not carry the risk of provoking drug-induced lupus syndrome. With the increased use of hydralazine over the past 5 to 10 years, it has become clear that avoidance of this serious immunologic reaction cannot be ensured by restricting dosage to an upper limit of 200 mg/day, and contrary to previous opinion, the kidneys do not always escape involvement.[35] I have successfully substituted nifedipine for hydralazine in several patients in whom the lupus syndrome prohibited continued treatment with the latter drug.

When good control of arterial pressure is achieved with the combination of a β blocker, diuretic and nifedipine, the diuretic can frequently be discontinued without more than a small increase in pressure. This emphasizes what may be the most important distinction between the calcium-entry blockers and other arteriolar dilators. Diazoxide and minoxidil cause such severe sodium retention that it is usually necessary to give high doses of loop diuretics concurrently; hydralazine causes less sodium retention, but it is, nevertheless, usually deemed necessary to give a diuretic with it. Verapamil and nifedipine do not normally cause sodium retention and, although diuretics may sometimes exert a useful additional hypotensive effect, their use is not mandatory.

The response to the first dose of a calcium-entry blocker is not always maintained with subsequent doses. One patient studied in this department had a decrease in pressure from 210/110 to 130/80 mm Hg after a single dose of 20 mg of nifedipine; however, during subsequent short-term treatment with 3 times daily dosage, the drug had little hypotensive effect. The emergence of tolerance does not, however, seem to be a problem during long-term therapy. In those patients who took part in our initial assessment of nifedipine, the response achieved after the first week or so of treatment has been maintained for periods in excess of 5 years.

The use of nifedipine in combination with captopril is currently being evaluated and it appears that it may have a useful role in resistant hypertension when given in this way. It certainly appears eminently sensible to combine inhibition of the potent extrinsic constrictor action of the renin-angiotensin system with inhibition of the intrinsic arteriolar tone.

Limited information is available concerning the antihypertensive effectiveness of calcium-entry blocking agents other than verapamil and nifedipine. Diltiazem, which resembles verapamil in its pattern of action, has been shown to decrease arterial pressure when given in short-[36] and long-term therapy.[37] Several dihydropyridines (the group to which nifedipine belongs) are being evaluated and it is to be hoped that new agents will be found that combine the therapeutic effectiveness of nifedipine with a longer duration of action and a lower incidence of subjective adverse effects.

In summary, the effectiveness of the calcium-entry blocking agents in the treatment of hypertension is now clearly documented; they may be used either alone or in combination with other hypotensive agents. They have advantages in some circumstances over such existing antihypertensives as β blockers and diuretics; they also offer advantages over other currently available dilators because they are free from the more serious adverse effects of the latter drugs. Nifedipine and, to a lesser extent, verapamil produce a significant incidence of subjective adverse effects, but after wide clinical use in patients with angina extending over many years, neither drug is known to cause hazardous adverse effects during long-term treatment. Further experience is required to evaluate the advantages and disadvantages of the calcium-entry blockers and to determine the extent to which they may usefully replace existing drugs in the treatment of hypertension.

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Effects of Calcium-Channel Blockers on Myocardial Preservation During Experimental Acute Myocardial Infarction

KEITH A. REIMER, MD, PhD, and ROBERT B. JENNINGS, MD

Calcium antagonists have become accepted agents for the attenuation of myocardial ischemia when it becomes manifest as angina pectoris. However, it is not known whether these agents can protect ischemic myocardium during the early evolution of an acute myocardial infarct. Calcium antagonists could potentially improve myocardial perfusion, by relieving coronary spasm or improving collateral blood flow, and reduce the energy demands of the ischemic myocardium either directly or by reducing heart rate or contractility. In some studies, calcium antagonists have decreased the rate of adenosine triphosphate depletion in ischemia and reduced functional or structural indexes of ischemic injury after relatively brief periods (up to 2 hours) of injury. We have assessed the ability of verapamil to protect severely ischemic myocardium in dogs with a 40-minute test period of circumflex occlusion followed by reperfusion. After 4 days of recovery, infarcts were sized by histologic methods. Untreated dogs had subendocardial infarcts (the more moderately ischemic subepicardial region being salvaged by reperfusion). Pretreatment with verapamil reduced the size of these subendocardial infarcts from 34 ± 8 to 8 ± 3% of the ischemic circumflex vascular bed (anatomic area at risk). Thus, verapamil prevented cell death in a substantial proportion of the severely ischemic subendocardial region that otherwise would have died as a result of the 40-minute test period of ischemia. To establish whether verapamil could prevent cell death for a longer period of time in the less severely ischemic subepicardial region, a 3-hour period of coronary occlusion with reperfusion was studied. This period of occlusion caused infarcts averaging 60 ± 6% of the ischemic area at risk in untreated dogs. Dogs treated with verapamil 15 minutes after occlusion and throughout the remaining 165 minutes of the 3-hour test period had no limitation of infarct size (53 ± 3% of the area at risk). In untreated dogs, infarct size was related inversely to baseline subepicardial collateral flow. Verapamil neither improved collateral flow nor altered the regression of infarct size versus blood flow. Thus, the early protective effect of pretreatment with verapamil was not sustained when ischemia was prolonged to 3 hours and when verapamil was given 15 minutes after the onset of ischemia. In experimental studies from other laboratories, calcium antagonists have had either a protective effect or no effect when infarct size was evaluated after ≥3 hours of coronary occlusion. Preliminary results of clinical trials with calcium antagonists in acute myocardial infarction have not been encouraging. The available experimental data indicate that calcium antagonists can prevent ischemic cell death during relatively brief periods of ischemia if reperfusion is established, but it is uncertain whether these agents can limit infarct size when ischemia is maintained for longer periods.

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The use of calcium antagonists for the attenuation of myocardial ischemia when it manifests as angina is widely accepted. There are many reports supporting the idea that calcium antagonists can delay the detrimental consequences of acute myocardial ischemia. However, it is not clear whether therapy with calcium antagonists can limit ultimate infarct size.

There are a number of hypothetical reasons why calcium antagonists might be beneficial to acutely ischemic myocardium. In the small subset of patients with infarction initiated by vasospasm,[1–3] relief of vasospasm by calcium antagonists could halt the evolution of an infarct.[4–6] A second reason for interest in calcium antagonists is the possibility of improved coronary collateral blood flow based on the known coronary vasodilating properties of those agents.[7] Third, peripheral vasodilation and decreased contractility reduce

From the Department of Pathology, Duke University Medical Center, Durham, North Carolina. This study was supported in part by Grants HL 23138 and 27416 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Keith A. Reimer, MD, PhD, Box 3712, Department of Pathology, Duke University Medical Center, Durham, North Carolina 27710.

myocardial metabolic demands. Fourth, it has been hypothesized that calcium overload may be instrumental in causing ischemic cell death[8] and calcium-entry blockers might delay or prevent this specific mechanism of cellular injury.

Early interest in the use of calcium antagonists in patients with myocardial infarction was stimulated by the observation that reperfusion of acutely ischemic myocardium was followed by so-called explosive cell swelling,[9] massive calcium overload with formation of myofibrillar contraction bands and myofibrillar disruption,[10] as well as by massive mitochondrial loading of calcium (Ca^{++}) with deposition of calcium phosphate densities[11] and consequent abolition of high energy phosphate production (Fig. 1). However, ultrastructural and tracer permeability studies suggest that the massive calcium overload in the setting of reperfusion occurs because of structural disruption of the plasmalemma of the myocyte[12–14] and is not primarily dependent on calcium specific channels (Fig. 2).

Nevertheless, as schematically illustrated in Figure 3, more subtle defects in calcium homeostasis may be detrimental early in the ischemic process, either by accelerating cellular utilization of adenosine triphos-

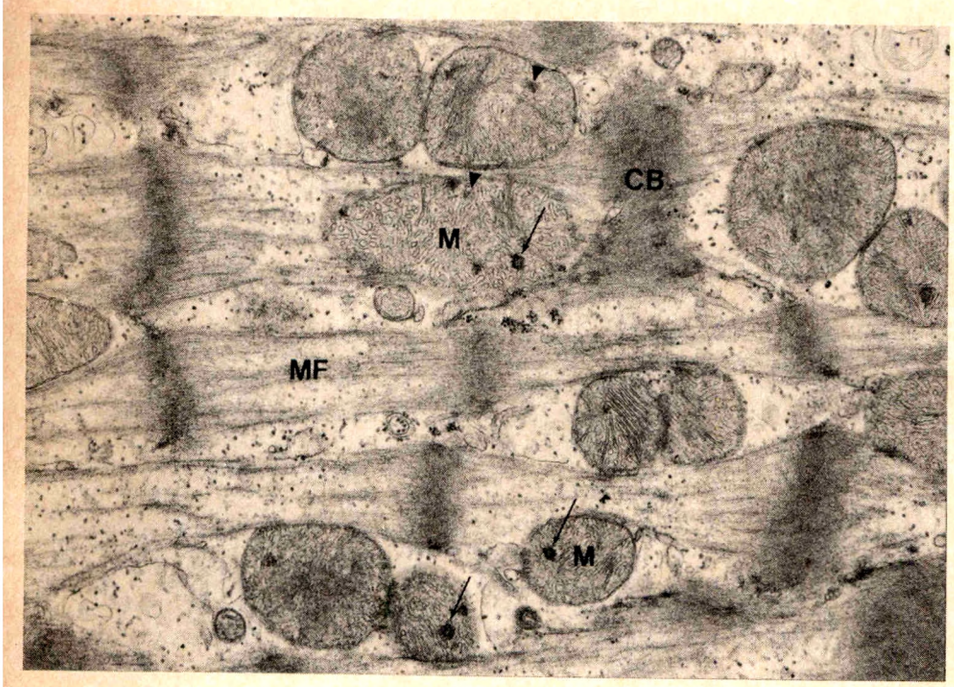

FIGURE 1. Ultrastructural features of contraction band necrosis in cardiac myocyte from subendocardial zone of ischemic region of dog heart after 40 minutes of coronary occlusion and 10 minutes of reperfusion. Myofibrils (MF) have been completely disrupted with myofibrillar proteins from several adjacent sarcomeres condensed into tangled masses referred to as contraction bands (CB). There has been massive influx of calcium into myocyte as evidenced by annular crystalline mitochondrial (M) densities (**arrows**) that have been shown to contain calcium and phosphate.[10,11] These changes, referred to as contraction band necrosis, are characteristic of myocardial cell death associated with ischemia and reperfusion. **Arrowheads** indicate amorphous matrix densities that are also characteristic of irreversible ischemic cell injury and can be seen before and after reperfusion.[12] Illustration from the work of Rocco et al.[83] Magnification × 22,000, reduced 29%.

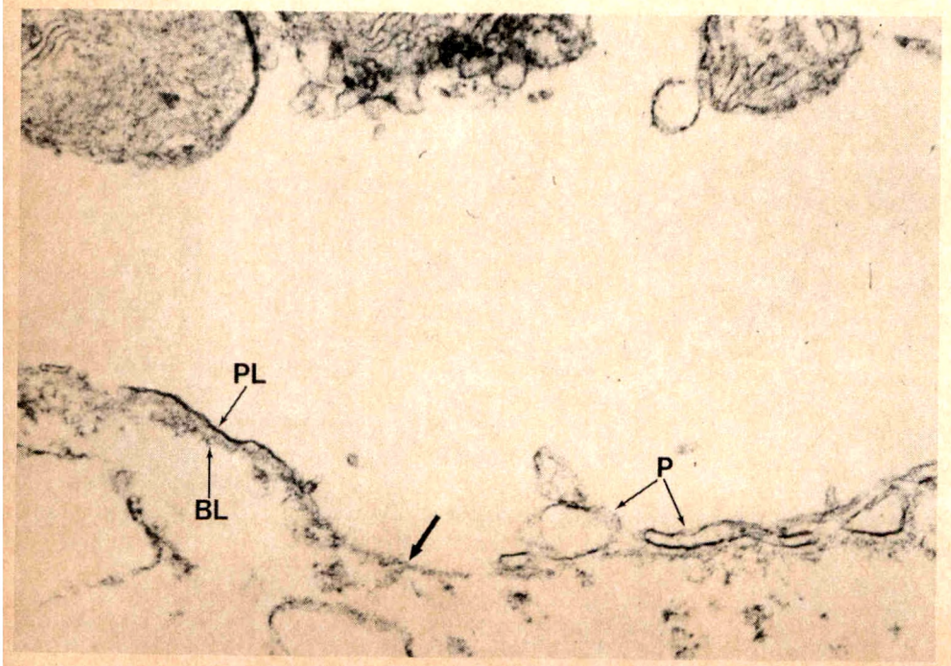

FIGURE 2. Sarcolemmal disruption observed in myocyte from subendocardial zone of ischemic region of dog heart after 40 minutes of coronary occlusion and 5 minutes of reperfusion. There is large edematous space (**central clear area**) separating sarcolemma from myofibrillar apparatus of myocyte. Sarcolemma is composed of basal lamina (BL) or glycocalyx and trilaminar unit membrane, plasmalemma (PL). Basal lamina appears intact but plasmalemma has been disrupted in some areas (for example **large arrow**) and has reformed as circular profiles (P) in other areas. Osmium tetroxide fixation; magnification × 69,000, reduced 28%. Reproduced with permission from *Am J Pathol.*[12]

phate (ATP) or by activating catabolic enzymes such as phospholipases, both of which might speed the onset of lethal cellular injury.[13] Thus, there are a number of reasons to speculate that calcium antagonists might protect ischemic myocardium.

The hypothesis that calcium antagonists protect ischemic myocardium has been tested in a large number of laboratories, using a variety of experimental models and different endpoints. We will review briefly some of the evidence accumulated in published reports, beginning with some of the more indirect experimental endpoints and following with direct studies of the effects of calcium antagonists on myocardial cellular injury and infarct size.

Studies in the mid- and late 1970s showed that calcium antagonists generally improved electrocardiographic indexes of injury in models of regional ischemia.[15–18] However, electrocardiographic improvement with nifedipine was dependent on dose,[18] and no electrocardiographic improvement was observed in cats with coronary occlusion treated with verapamil.[17]

Calcium antagonists have had variable but generally positive effects on contractile function of ischemic segments during acute coronary occlusion[19–22] and have improved postischemic recovery of function in models of global or regional ischemia followed by restoration of coronary perfusion.[23–37] The latter results have been of particular interest with respect to the possible use of calcium antagonists as cardioplegic agents during cardiac surgery.

More direct indexes of cell damage such as mitochondrial function,[37–41] myocardial calcium accumulation[42] or enzyme release,[18,25,43–46] gross or histologic myocardial necrosis[47–49] and ultrastructural changes[32–38] also have been studied in various models of global or regional ischemia or hypoxic perfusion. These studies have all involved relatively brief periods of injury, that is, ≤2 hours under normothermic conditions. Most of these published reports have shown that calcium-channel blockade, either with verapamil, nifedipine or diltiazem, reduced the deleterious effect of ischemia over the time period studied.

If calcium antagonists can delay the cellular consequences of ischemia and can protect ischemic myocardium for relatively brief periods of time, can they also limit infarct size when ischemia is more prolonged? Several laboratories have published results of therapy with calcium antagonists in experimental animals, during longer periods of ischemia.

Karlsberg et al[50] evaluated verapamil therapy begun 5 hours after coronary occlusion in an awake dog model. Verapamil failed to limit infarct size, as measured by myocardial creatine kinase (CK) depletion 24 hours after coronary occlusion. However, in dogs with acute coronary occlusions, most of the myocardium that will undergo infarction has already died by 3 hours[51,52] and it is likely that little potentially salvageable ischemic myocardium remained at the time therapy was started in their study.

At least 5 studies have shown limitation of experimental infarct size with calcium antagonists, when measured at times ranging from 6 hours to 2 days after coronary occlusion. Henry et al[53] showed less CK loss from 24-hour-old infarcts that had been induced by coronary occlusion in awake dogs and treated with nifedipine beginning 30 minutes after coronary occlusion. DeBoer et al[54] observed smaller infarcts, as estimated grossly, 8 hours after occlusion, using triphenyl tetrazolium chloride (TTC) staining in anesthesized dogs in which verapamil therapy was started 1 hour after occlusion. Zamanis et al[55] showed a reduction in histologic infarct size in rats with 48-hour coronary occlusions treated with diltiazem. Alps et al[56] achieved marked limitation of infarct size with a newer calcium antagonist, nicardipine, in baboons. In this study, infarct size was assessed grossly based on para-nitroblue tetrazolium staining 6 hours after coronary occlusion. Infarct size was normalized for the area at risk, which was assessed from x-rays of ventricular slices after postmortem injection of the coronary arteries with contrast material. Most dramatically, Yellon et al[57] have observed marked limitation of infarct size, measured grossly, based on TTC staining 24 hours after coronary occlusion in dogs treated with verapamil.

In contrast, Alps et al[56] showed no effects of verapamil or nifedipine on infarct size when evaluated using the same protocol used to study nicardipine. Also, Geary et al[58] showed no effect of nifedipine in baboons when infarcts were caused by 2 hours of coronary occlusion followed by reperfusion.

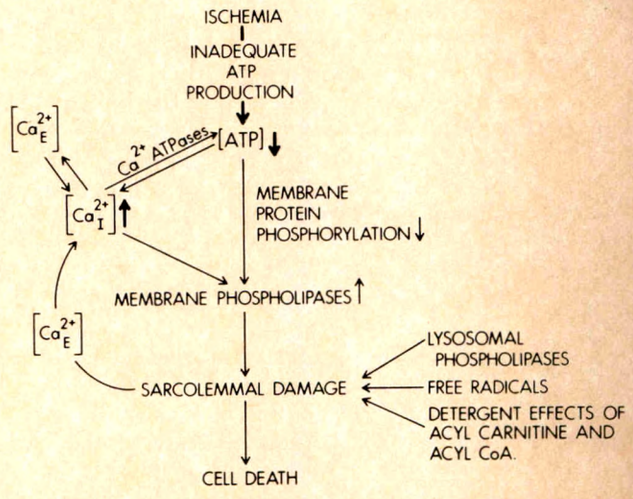

FIGURE 3. Potential relations between adenosine triphosphate (ATP) depletion, calcium influx and sarcolemmal damage, which forms basis for various hypotheses of events leading to sarcolemmal damage. ATP of ischemic myocytes decreases because ATP utilization exceeds capacity of anaerobic glycolysis to produce high energy phosphates. Intracellular calcium (Ca_I^{2+}) may increase either because of increased membrane permeability to calcium or because of inadequate ATP to support mechanisms responsible for calcium extrusion from cell or sequestration of calcium by sarcoplasmic reticulum. Increased Ca_I^{2+} also may accelerate ATP depletion through calcium-activated ATPases. Sarcolemmal damage occurs at ATP levels of 3 to 8% of control. Mechanism of damage is unknown. One explanation is activation of endogenous sarcolemmal phospholipases by increased Ca_I^{2+} or depressed phosphorylation of membrane proteins that ordinarily inhibit activity of endogenous phospholipases of sarcolemma. Lysosomal phospholipase release, free radicals or detergent action of acyl carnitine or acyl coenzyme A (CoA) are also possible causes of sarcolemmal damage in myocardial ischemia. Reproduced with permission from *Am J Pathol.*[13]

TABLE I **Hemodynamic Parameters* Measured 20 Minutes Postocclusion in Control- and Verapamil-Treated Dogs with 40 Minutes of Circumflex Artery Occlusion**

	Dogs (n)	Heart Rate (beats/min)	MBP (mm Hg)	LVSP (mm Hg)	LVEDP (mm Hg)
Control	6	174.0 ± 5.0	119.0 ± 9.4	147.0 ± 11.0	9.3 ± 2.7
Verapamil	8	136.0 ± 4.2*	86.0 ± 3.4*	123.0 ± 2.0	10.9 ± 2.3

Values are means ± standard error of the mean.
* $p < 0.01$.
LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; MBP = mean blood pressure.

TABLE II **Coronary Blood Flow to Nonischemic and Ischemic Myocardium Measured 20 Minutes After Occlusion in Control- and Verapamil-Treated Dogs with 40 Minutes of Circumflex Artery Occlusion**

	Dogs (n)	Control (ml/min/g)	LAD % Control	Circumflex		
				I	M	O
Control	6	1.72 ± 0.16	102.0 ± 10.1	4.8 ± 1.2	11.3 ± 1.1	22.2 ± 2.3
Verapamil	8	1.48 ± 0.12	153.0 ± 20.1*	4.3 ± 1.3	8.7 ± 1.0	14.6 ± 1.8

Values are means ± standard error of the mean.
* $p < 0.05$.
I = inner (subendocardial); LAD = left anterior descending nonischemic arterial region; M = middle, O = outer (subepicardial) zones of the ischemic region.

We have used 2 models for testing the effects of an intervention on myocardial ischemic injury and infarct size.[47,59–63] These models use anesthetized open-chest dogs with temporary occlusions of the circumflex artery. In this species, ischemic myocardium does not all undergo infarction simultaneously but there is a transmural progression of injury (Fig. 4).[63] By 40 minutes, the most severely ischemic subendocardial region is irreversibly injured but the more moderately ischemic subepicardial region is still viable. By 3 hours, much of this moderately ischemic zone also is irreversibly injured and reperfusion at this time results in infarcts only slightly smaller than infarcts caused by permanent coronary occlusion.[63]

In one model, we tested the effect of interventions on the amount of necrosis induced by a 40-minute test period of ischemia. In this test system, moderately ischemic subepicardial myocardium is spared by reperfusion,[63] irrespective of treatment; the question is whether therapy can delay injury in severely ischemic myocardium for the 40-minute duration and thereby prevent or reduce the size of subendocardial infarcts. In the other model, therapy was given during 3 hours of ischemic injury. Although the subendocardial region would probably be beyond salvage in this test system, we wanted to determine whether cell injury could be delayed in the moderately ischemic subepicardial myocardium.[61–63] We also wanted to see if the transmural extent of these infarcts could be limited. We tested verapamil in both models.[62]

In the 40-minute test system, we administered verapamil before coronary occlusion. After 40 minutes of ischemia, reperfusion was established. The primary endpoint was infarct size, measured histologically 4 days after the acute event. The secondary endpoints measured were the baseline variables that influence infarct size: collateral blood flow, which was measured with tracer microspheres, anatomic size of the occluded vascular bed, which was measured by postmortem coronary dye injections, and hemodynamic parameters which influence myocardial metabolic requirements. Heart rate, mean blood pressure and left ventricular (LV) systolic pressure all were reduced in the verapamil-treated group but LV end-diastolic pressure was unchanged (Table I). Compared with blood flow before drug administration, verapamil caused a 50% increase

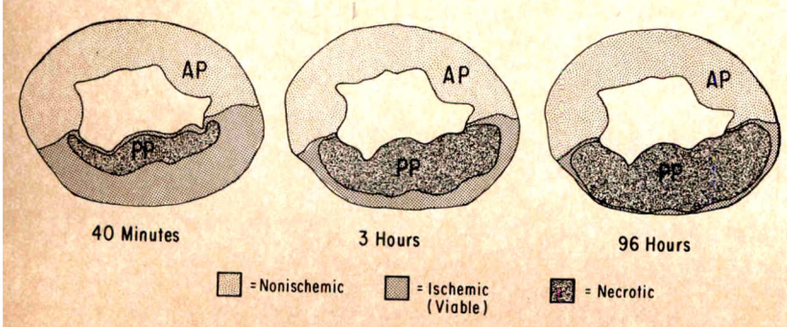

FIGURE 4. Progression of cell death versus time after left circumflex coronary artery occlusion. Necrosis occurs first in subendocardial myocardium. With longer occlusion, wavefront of cell death moves from subendocardial zone across wall to involve progressively more of transmural thickness of ischemic zone. In contrast, lateral margins in subendocardial region of infarct are established as early as 40 minutes after occlusion and are sharply defined by anatomic boundaries of the ischemic bed. AP = anterior papillary muscle; PP = posterior papillary muscle. Reproduced with permission from *Lab Invest.*[63]

in myocardial blood flow in nonischemic myocardium. Collateral blood flow averaged 5, 11 and 22% of control in the subendocardial, mid- and subepicardial regions of ischemia in control animals and was slightly less in dogs given verapamil (Table II).

Forty minutes of ischemia in untreated dogs caused subendocardial infarcts that averaged 13% of the left ventricle and 34% of the occluded circumflex vascular bed (Table III). Despite the somewhat worse myocardial perfusion during ischemia, verapamil markedly reduced necrosis to 3% of the left ventricle and 8% of the ischemic vascular bed. Thus, in this particular experimental model, verapamil had a dramatically positive effect on ischemic myocardium, and clearly delayed the onset of cell death. These results are consistent with results of the several other studies showing protective effects of calcium antagonists during relatively brief periods (≤2 hours) of myocardial ischemia or hypoxia.

The mechanism for early protection by calcium antagonists is not established. One possibility is improved collateral blood flow. However, verapamil did not improve collateral flow in our experiments. Also, in models of global ischemia in which there is no collateral flow, improved collateral blood flow clearly is not involved in the cardioprotective effects. In other studies of regional ischemia, the effects of calcium-channel blockade on coronary collateral flow have been variable. Several laboratories in addition to our own have observed no improvement in collateral flow with various calcium antagonists in dogs with complete coronary occlusion.[22,50,64–67] Other studies have observed improved blood flow in samples with initially moderately reduced flow.[53,68–70] However, these results showing improved collateral flow can most likely be explained by the failure to identify the interface between ischemic and nonischemic regions, with consequent inclusion of nonischemic myocardium in some ischemic samples.

It seems more likely that the protective effects of calcium antagonists are due to direct cellular actions. In this regard, it has been demonstrated in several studies that calcium antagonists do reduce the rate of high energy phosphate depletion during ischemic or hypoxic injury.[24,38,40,71,72] Figure 5 nicely illustrates 2 hypotheses regarding possible mechanisms of protection.[40] Inhibition of calcium influx may result either directly or indirectly in a reduction of myocardial ATP utilization. This may be beneficial either by better maintenance of calcium homeostasis and prevention of calcium overload, or through maintenance of other ATP dependent processes, the absence of which could be lethal. Previous studies have shown a close relation between marked depletion of ATP and the adenine nucleotide pool and the onset of lethal myocardial ischemic cell injury.[13,73]

We used a 3-hour period of ischemia to evaluate whether verapamil can prevent infarction in areas of myocardium that are more moderately ischemic.[62] By 3 hours, most of the myocardium that would become infarcted with a permanent coronary ligation is already dead and reperfusion at this time achieves at best only about a 10% limitation in infarct size.[63] If therapy during a 3-hour occlusion is successful, it will limit a potentially transmural infarct to one which is subendocardial.[61,63] Drug therapy or saline (control) was begun 15 minutes after coronary occlusion and continued through the 3-hour test period of ischemia. After 3 hours, reperfusion was established and the dogs were allowed to live 4 days. As with the 40-minute model described previously, the major endpoint was infarct size, quantitated from histologic sections. Again, baseline variables that influence infarct size—size of the ischemic vascular bed, collateral blood flow and hemodynamic parameters—were measured.

TABLE III Area at Risk and Infarct Size in Control- and Verapamil-Treated Dogs with 40 Minutes of Ischemia and 4 Days of Reperfusion

	Dogs (n)	Size of LCC Bed	Necrosis % of LV	Necrosis % of LCC Bed
Control	6	39.9 ± 1.8	13.0 ± 2.8	34.3 ± 8.0
Verapamil	8	38.6 ± 2.1	3.1 ± 1.6*	8.1 ± 2.9*

Values are means ± standard error of the mean.
* $p < 0.01$.
LCC bed = occluded circumflex coronary region at risk of infarction; LV = left ventricle.

In this study, heart rate and blood pressure were both reduced somewhat by verapamil but cardiac output was maintained and LV end-diastolic pressure was not different between the verapamil and the control groups (Fig. 6). Verapamil caused a significant increase in blood flow to nonischemic myocardium but did not improve subendocardial or subepicardial collateral blood flow in the ischemic zone.

In comparison to the dramatically positive results with verapamil in the 40-minute model, infarct size was

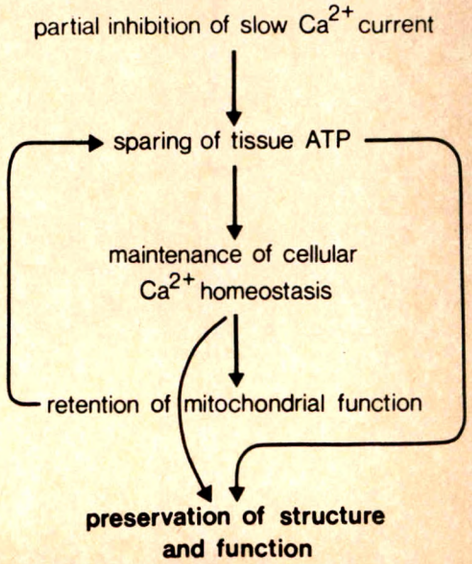

FIGURE 5. Schematic representation of possible pathways involved in protective effect of drugs inhibiting slow channel calcium transport (calcium antagonists). Reproduced with permission from *Am J Cardiol.*[40]

not reduced by verapamil in the 3-hour study (Fig. 7). This negative result was observed when infarct size was expressed as a percentage of the left ventricle or as a percentage of the anatomic area at risk. In addition, the transmural extent of the infarct was not altered.

Because collateral blood flow is such an important determinant of infarct size,[51,63,74] infarct size results should be carefully examined in comparison to this variable. Subendocardial infarctions always develop in untreated dogs, but the subepicardial region may be involved to a variable extent and there is an inverse correlation between the transmural extent of the infarct and collateral blood flow to the subepicardial myocardium.[63] One way to incorporate measurements of collateral blood flow into the analysis of infarct size is illustrated in Figure 8.[61–63] With any therapy that limits infarct size, infarcts must be smaller than predicted from a baseline (pretreatment) measurement of collateral flow. Thus, successful limitation of infarct size would alter the regression of infarct size (as a percentage of area at risk) versus baseline subepicardial collateral flow. In addition, when the regression of infarct size on pre- versus posttreatment measures of infarct size are compared, information can be gained about the mechanism of the protective effect. Drug therapy that limits infarct size must do so either by improving collateral blood flow or by having beneficial effects on metabolism or structural integrity of the ischemic myocyte despite continued ischemia.[75] With therapy that affords metabolic or structural protection without effect on collateral flow, the regression of infarct size versus collateral flow would be displaced downward from the control relation (Fig. 8, left). Conversely, therapy that alters collateral flow would shift points along the curve when a posttreatment measure of flow is used (Fig. 8, right).

The relation between infarct size and flow is illustrated for control infarcts in Figure 9, top, and for verapamil-treated infarcts in Figure 9, bottom.[62] At most, 2 of 11 verapamil-treated infarcts were smaller than expected from baseline measurement of collateral blood flow, and verapamil may have provided protec-

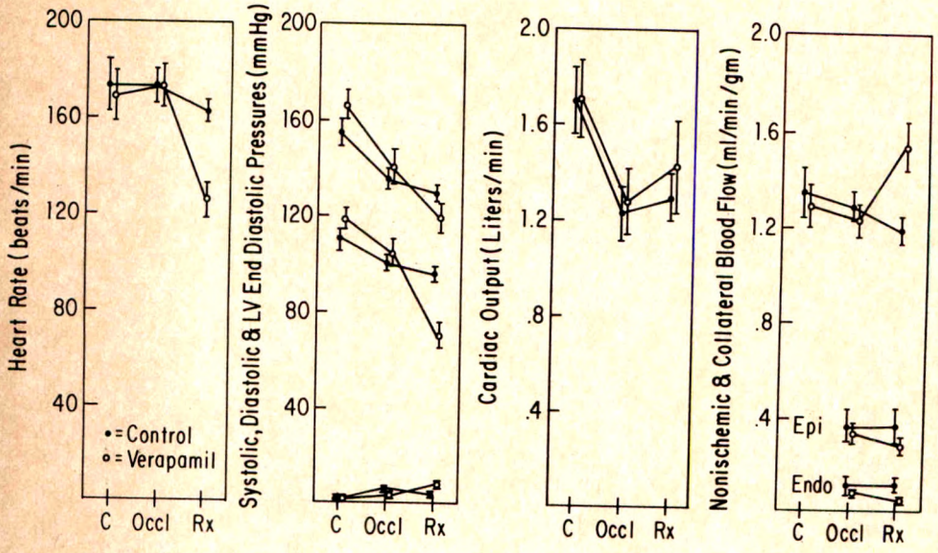

FIGURE 6. Effects of coronary occlusion and verapamil therapy on hemodynamic parameters and regional blood flow. Measurements were made before occlusion (C), after occlusion but before treatment (Occl) and after treatment (Rx). Heart rate and blood pressure both were reduced somewhat by verapamil but cardiac output was maintained and left ventricular end-diastolic pressure was not different between control (**closed circle**) and verapamil-treated (**open circle**) groups. Verapamil caused significant increase in blood flow to nonischemic myocardium but did not improve subendocardial (Endo) or subepicardial (Epi) blood flow in ischemic zone. Reproduced with permission from *Lab Invest.*[62]

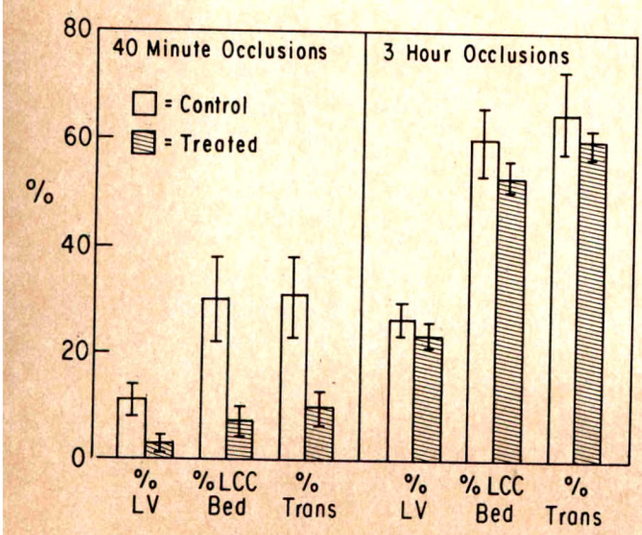

FIGURE 7. Effect of verapamil on myocardial infarct size induced by 40 minutes versus 3 hours of temporary coronary occlusion. Verapamil had dramatically positive effects when tested in 40-minute model (**left**), but in 3-hour study (**right**), infarct size was not reduced by verapamil. Latter negative result was observed when infarct size was expressed as percentage of left ventricular (LV) or as percentage of anatomic area at risk (percent left circumflex coronary [LCC] bed). In addition, transmural (trans) extent (percent transmural) of infarct was not altered. Reproduced with permission from *Lab Invest.*[62]

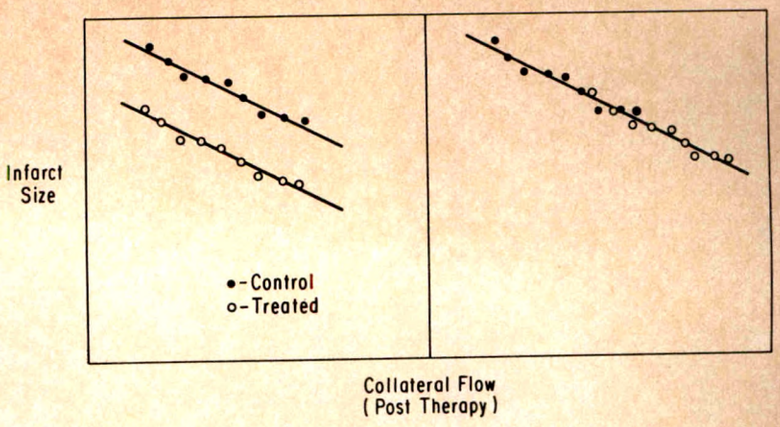

FIGURE 8. Hypothetical results of ideal experiment to illustrate how relation between infarct size and collateral blood flow can be used to evaluate effects of therapy. With any therapy that limits infarct size, infarcts would be smaller than predicted by baseline collateral flow measurement, and regression of infarct size versus flow would shift downward. With intervention that does not alter collateral blood flow, regression line of infarct size versus flow also would shift downward when posttreatment measurements of flow is used (**left**). Conversely, intervention that limits infarct size by improving collateral blood flow would shift points to right along control regression line when posttreatment measurement of flow is used (**right**). Thus, incorporation of collateral flow measurements should permit detection of positive effect with greater precision and provide information about mechanism of treatment effect.

tion. The possibility that metabolic protection was obscured by the slight decrease in collateral blood flow was excluded because the regression using the posttreatment measure of collateral flow (obtained 1 hour after coronary occlusion) was similar to that shown in Figure 9, bottom.

These results have been confirmed in a considerably larger number of dogs as part of a National Institutes of Health collaborative study (the AMPIM study)[76] in which verapamil was simultaneously reevaluated in our laboratory and in the laboratories of Becker at Johns Hopkins and Cobb at the Duke Veterans Administration. The major endpoints were similar in all 3 studies. The Hopkins and Veterans Administration studies differed from ours in that we used a reperfusion model, while they used awake, chronically instrumented dogs with permanent coronary occlusions. All 3 laboratories in this collaborative effort showed no effect of verapamil on infarct size.

Why calcium antagonists show protective effects in some studies but not in others is not known. It is possible that different results may be due to differences among the individual drugs, the dose regimens or the different responses to therapy among different animal models. However, it is clear that in all animal models of myocardial infarction, infarct size is influenced by a number of biologic variables unrelated to therapy per se. All of the studies reporting limitation of infarct size with calcium-antagonist therapy during ≥6 hours of ischemia have failed to consider 1 or more of the important determinants of infarct size, such as the size of the anatomic area at risk or the baseline collateral blood flow measurement.[51,63,74,77,78] Thus, uncontrolled differences among treated and untreated animals may have occurred and caused false-positive results. In addition, we postulate that the markedly positive results in the study of Yellon et al[57] may have been due to the peculiarities of the model used: coronary occlusion was achieved by injecting a small plug into the coronary arteries and the coronary vasodilating action of the verapamil may have caused distal migration of the plug.

Relatively little information is available regarding the effect of calcium antagonists on myocardial infarct size in patients. The results of 2 separate clinical trials using

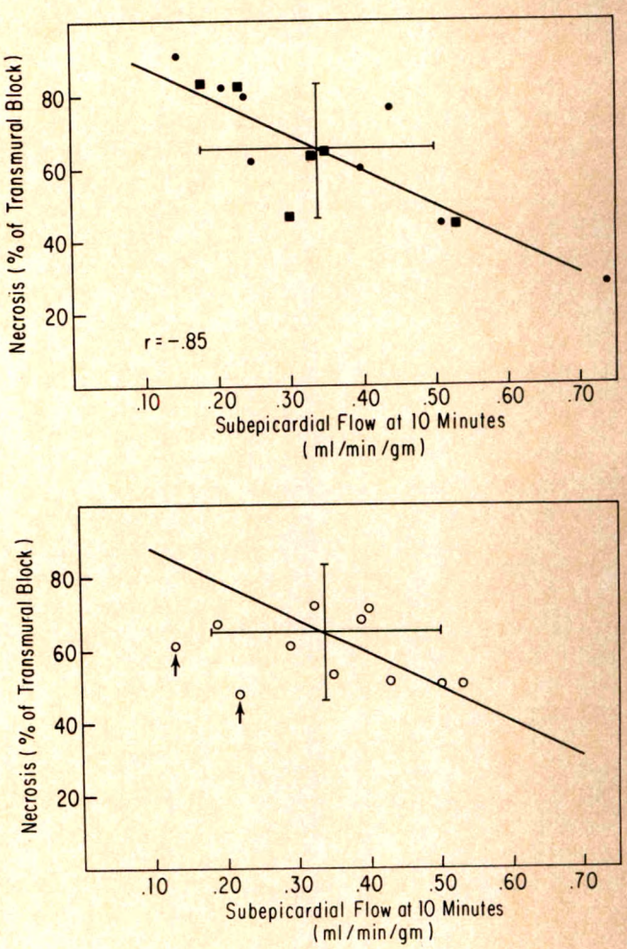

FIGURE 9. Relation between transmural extent of infarction after 3 hours of coronary occlusion and collateral blood flow in subepicardial region is shown for untreated dogs (**top**) and verapamil-treated dogs (**bottom**). In the top panel, **solid circles** represent control dogs from this study and **solid squares** represent dogs studied using identical protocol for another unpublished study. Strong inverse relation ($r = -0.85$) between extent of infarct and intrinsic collateral flow shows that collateral flow is important determinant of infarct size. Bottom panel shows best fit line and standard deviations from control group illustrated in top panel, but control points have been replaced by verapamil points. Even when considered in relation to collateral blood flow, verapamil, with 2 possible exceptions (**arrows**), had no effect on infarct size. This analysis is based on collateral flow measured after coronary occlusion but before administration of verapamil. Reproduced with permission from *Lab Invest.*[62]

nifedipine in patients with acute myocardial infarctions have been reported to date. In the Norwegian trial,[79] infarct size, assessed by plasma CK curves, was similar in both nifedipine-treated and control groups. No protective effect was observed even when analysis was limited to patients who were treated within 3 hours of onset. Muller et al[80] reported that nifedipine did not alter the incidence of myocardial infarction in patients admitted with threatened myocardial infarction nor did it limit CK estimates of infarct size in patients admitted because of either overt or threatened myocardial infarction.

In summary, it is clear from much accumulated evidence that calcium antagonists, including verapamil, delay the early progression of ischemic injury. Calcium-channel blockers delay the depletion of high energy phosphates as well as other metabolic consequences of ischemia. However, the mechanism of the initial prevention of ischemic cell injury is not established. It is possible that inhibition of calcium influx through the calcium channels delays a calcium overload. Most evidence suggests that calcium blockers do not improve collateral blood flow in models of regional ischemia.

Because of early protection, calcium antagonists may be beneficial as adjuncts to cardioplegia during cardiac injury. Extrapolation of experimental results to clinical settings must be done with caution because the pathogenesis of myocardial infarction in man is complex and still not fully understood. Several possible causes of infarction may occur singly or in combination. Many infarcts are the result of acute thrombotic occlusion of previously stenotic vessels.[81,82] Others may be precipitated by spasm,[1,2] by hemodynamic or neurogenic factors or by platelet aggregation[3] superimposed on chronic atherosclerotic disease. In patients with abrupt coronary occlusion and few preformed collateral vessels, myocardial infarction might evolve to rapid completion in a time frame similar to that observed in our studies in dogs. In patients with extensive preformed collateral vessels or with incomplete or intermittent coronary occlusion, infarction might occur more slowly or intermittently.

Many of the experimental models of infarction reviewed here are most analogous to the clinical situation in which abrupt and fixed coronary occlusion occurs in a heart with some but relatively few preformed collateral vessels. Calcium antagonists administered after the onset of ischemia would clearly be most beneficial in those few patients whose infarction was initiated by vasospasm that could be abolished by these drugs. Whether calcium antagonists can delay myocardial cell death in patients with fixed coronary occlusion is uncertain, but it seems likely that such therapy would not prevent myocardial cell death indefinitely in the absence of early reperfusion. Our results suggest that the best chance for limitation of infarct size would occur in those patients who had been treated on a long-term basis with calcium antagonists and in whom either spontaneously or therapeutically induced reperfusion occurred relatively early after the onset of acute coronary occlusion.

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Calcium Antagonists for Acute Ischemic Heart Disease

MICHAEL D. WINNIFORD, MD, JAMES T. WILLERSON, MD, and L. DAVID HILLIS, MD

The pharmacologic and physiologic effects of the slow-channel calcium antagonists verapamil, nifedipine and diltiazem are reviewed. Relevant pathophysiologic features of various acute ischemic heart disease syndromes are also reviewed and the clinical applications of the slow-channel calcium antagonists to acute ischemic heart disease syndromes in patients are discussed.

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The slow-channel calcium antagonists verapamil, nifedipine and diltiazem dilate coronary arteries and increase coronary blood flow but exert varying effects on heart rate, atrioventricular (AV) nodal conduction and myocardial contractility.[1–3] The purpose of this review is 2-fold: to describe the pharmacologic and physiologic effects of these agents, and to identify their role in the treatment of patients with acute ischemic heart disease, including Prinzmetal's, or variant, angina pectoris, unstable angina pectoris and acute myocardial infarction.

Physiologic Considerations

Calcium ions play a central role in modulating myocardial contractility and vascular smooth muscle tone (Fig. 1 and 2). In cardiac myocytes, the action potential initiates a slow inward movement of calcium through specialized sarcolemmal channels (so-called slow calcium channels), and this calcium current is responsible for the plateau phase of the action potential. In turn, the small amount of calcium entering the myocyte through the slow calcium channels (and by other mechanisms) causes the release of larger amounts of calcium from intracellular storage sites, primarily the sarcoplasmic reticulum (Fig 1).[4] The calcium that is released from intracellular storage sites is bound to the regulatory protein troponin, leading to the interaction of actin-myosin and resultant sarcomere shortening. Pharmacologic antagonism of the slow calcium channels interferes with excitation-contraction coupling, thus diminishing myocardial contractility.

From the Department of Internal Medicine (Cardiology Division) at the University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas. This study was supported in part by Ischemic SCOR Grant HL-17669 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and by the Moss Heart Fund, Dallas, Texas.

Address for reprints: James T. Willerson, MD, Ischemic Heart Center, Room L5.134, the University of Texas Health Science Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

In vascular smooth muscle, changes in vascular tone depend on the movement of calcium from the extracellular to the intracellular space (Fig. 2),[5,6] where it is bound to the regulatory protein calmodulin.[7,8] The calcium-calmodulin complex activates myosin light chain kinase, resulting in smooth muscle contraction. A decrease in transsarcolemmal calcium entry reduces smooth muscle tone and causes vasodilation. The mechanism by which the slow-channel calcium antagonists inhibit transsarcolemmal calcium influx is unknown. Binding studies with both the dihydropyridine (nitrendipine and nifedipine) and nondihydropyridine calcium antagonists (verapamil and diltiazem) have indicated different myocardial sarcolemmal binding sites or different affinities for binding or both.[9,10]

Pathophysiologic Features of Acute Ischemic Heart Disease Syndromes

Prinzmetal's (variant) angina pectoris is characterized by angina at rest, ST-segment elevation during chest pain, spasm with focal obliteration of the lumen of a large or medium-sized coronary artery and alleviation of chest pain and ST-segment elevation as the spasm resolves (Fig. 3).[11,12] This entity should be suspected in the patient who has angina primarily at rest and the diagnosis should be confirmed by obtaining an electrocardiogram during chest pain.[13] Additional clinical features may include episodic variations in anginal activity, angina with exercise and the occurrence of coronary arterial spasm in a small coronary artery, resulting in ST-segment depression and T-wave inversion. Ergonovine maleate provokes coronary arterial spasm during periods of anginal activity in susceptible persons.[14,15]

The causes of coronary arterial spasm are unknown, but several have been suggested, including increases in the local concentration of thromboxane A_2,[16] vasopressin[17] or histamine[18]; damage to the coronary endothelium and subsequent vasoconstrictor responses to a variety of agonists[19–21]; and diminished production

or sensitivity to the vasodilator prostaglandin prostacyclin. About 20% of patients with Prinzmetal's angina have angiographically normal or minimally diseased coronary arteries, whereas the remainder have significant coronary arterial stenoses; therefore, some patients may have 2 mechanisms responsible for angina: a decrease in myocardial oxygen delivery (caused by coronary spasm) and a relative increase in myocardial oxygen demand associated, for example, with stress and exercise.

Unstable angina pectoris is characterized by increasingly frequent episodes of angina with lesser degrees of effort; in most patients, angina also occurs at rest.[22,23] Most of these patients have physiologically significant coronary arterial stenoses, although the extent of coronary disease varies widely.[24] The major pathophysiologic mechanism responsible for this syndrome is a decrease in myocardial oxygen delivery,[25] which may be caused by coronary arterial spasm,[25] platelet aggregation at sites of critically narrowed coronary arteries (Fig. 4 and 5),[16,26,27] or a progressive decrease in coronary arterial luminal diameter. Thus, it should be possible for several different causes of abrupt and progressive alterations in coronary arterial luminal diameter to lead to angina pectoris at decreasing levels of effort or rest or both. Theoretically, pharmacologic interventions that improve coronary blood flow through such stenotic arteries should help alleviate this clinical problem. Such interventions might include nitrates, selected calcium antagonists, agents that interfere with platelet aggregation, coronary arterial revascularization, or some combination of these.

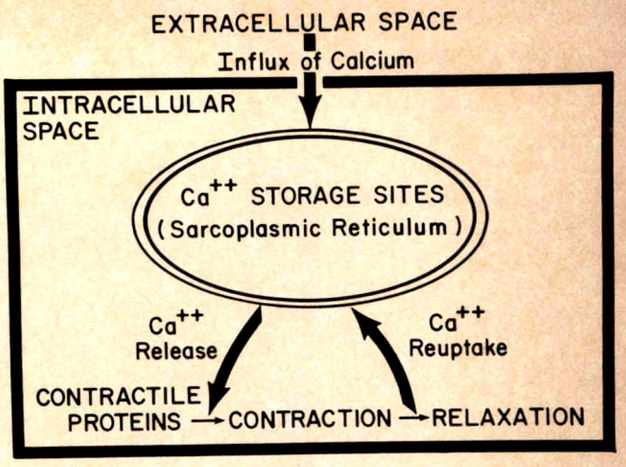

FIGURE 1. Schematic representation of role of calcium (Ca^{++}) in regulating myocardial contractility and vascular smooth muscle tone. After entering the cell, calcium is stored in the sarcoplasmic reticulum, from which it is periodically released and binds to contractile proteins, leading to contraction. Influx of calcium into the cell and its subsequent release from sarcoplasmic reticulum occur through slow channels and, therefore, are inhibited by the slow-channel calcium antagonists. Reproduced with permission from *Angiology*.[1]

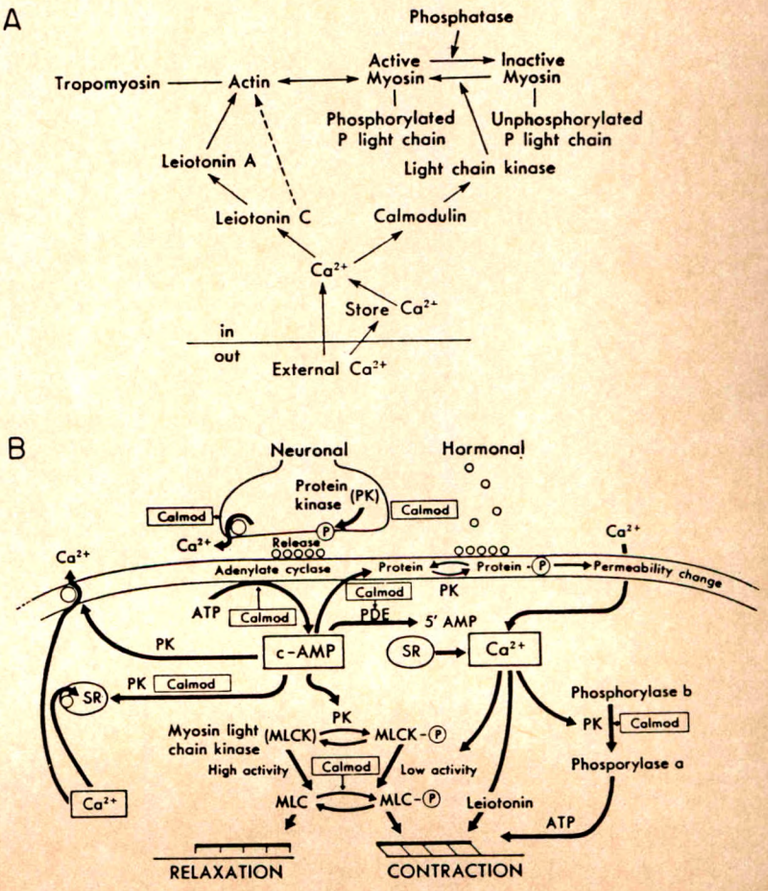

FIGURE 2. Calcium's role in regulating myocardial contractility and vascular smooth muscle tone. Two different concepts for calcium (Ca^{2+}) regulation, leiotonin C (**A**) and calmodulin (**B**), are shown. **Solid arrows** indicate direction of binding, interaction and activations. **A, dashed arrow** suggests possibility of binding protein (17-k dalton acidic protein) that is distinct from calmodulin. Ca^{2+} initiates the actin-myosin interaction by binding to leiotonin C, which itself interacts with leiotonin A (85-k dalton substance, actin-binding protein) and tropomyosin, causing actin-activation of myosin ATPase activity. Other hypothesis (**B**) ("calmodulin hypothesis") suggests that Ca^{2+} triggers actin-myosin interaction by binding to calmodulin, which then activates the kinase catalyzing phosphorylation of myosin, required for actin activation. Reproduced with permission from *Am J Physiol* 1982;243:H653. ATP = adenosine triphosphate.

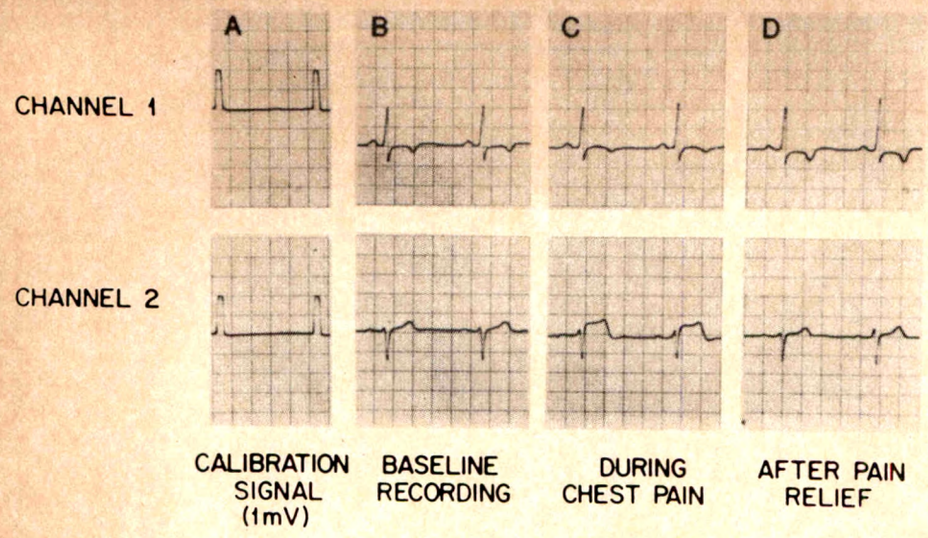

FIGURE 3. Calibrated Holter monitor recordings in patient with Prinzmetal's (variant) angina pectoris. At baseline, ST segments appear normal. During chest pain, ST-segment elevation of 2 to 3 mm occurs in channel 2. After pain relief, ST segments return to baseline, and there is no evidence of infarction (no Q waves or loss of R-wave voltage). Reproduced with permission from Willerson JT, Hillis LD, Buja LM. *Ischemic Heart Disease: Clinical and Pathophysiological Aspects.* New York: Raven Press, 1982:85.

Acute myocardial infarction that is transmural is usually caused by coronary arterial thrombosis, often occurring as a consequence of hemorrhage into an atherosclerotic plaque.[28,29] However, postmortem examinations have suggested that coronary arterial thrombosis occurs in only approximately 30% of patients with acute subendocardial infarcts.[28] Instead, acute subendocardial infarction may be caused by a profound increase in myocardial oxygen demand in a patient with severe coronary arterial stenoses or a prolonged decrease in myocardial oxygen delivery or both, such as might occur with coronary arterial spasm, platelet aggregation at the site of a severely narrowed coronary artery, hemorrhage into an atherosclerotic plaque with subsequent thrombosis, progressive coronary arterial luminal diameter narrowing, or some combination of these.[28]

Pharmacologic Considerations

Because the slow-channel calcium antagonists cause peripheral and coronary vasodilation,[2] they may decrease systemic arterial pressure, afterload and myocardial oxygen demand. In response to this, a reflex increase in coronary vascular resistance may occur, resulting in increase, decrease or no change in coronary blood flow. In isolated cardiac muscle, each of these agents depresses contractility in a dose-dependent manner,[30] but the magnitude of this decrease in patients depends on the slow-channel calcium antagonist used

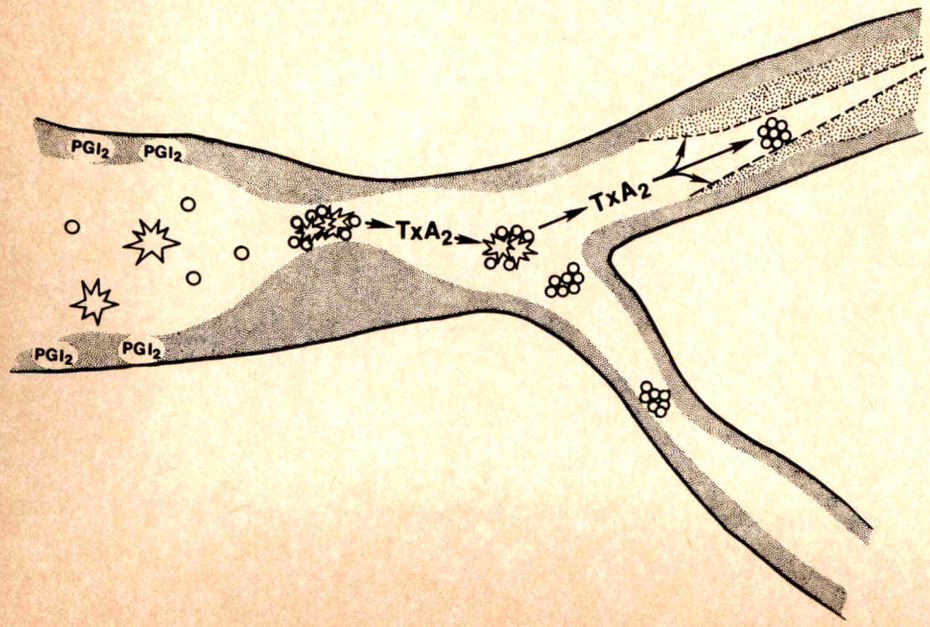

FIGURE 4. Schematic representation of manner in which episodic platelet aggregation may occur at the site of severe coronary arterial narrowings, causing unstable angina pectoris. Actively aggregating platelets accumulate at site of a stenosis, releasing thromboxane TxA_2, a powerful promoter of platelet aggregation. Periodically, these platelet aggregates fragment and move distally past severe stenosis, where they lodge in smaller arterioles and capillaries. **Open circles** designate platelets; **stars,** aggregated platelets. Reproduced with permission from *Am J Med.*[27]

and the dosage administered, as well as the magnitude of decrease in afterload, which, if prominent, may mask a negative inotropic effect. With reductions in afterload, there may be an increase in sympathetic tone, such that cardiac output is unchanged or increases slightly; heart rate may also increase reflexly.[31–34]

Verapamil has been used for the treatment of ischemic heart disease and supraventricular tachyarrhythmias since the 1960s.[32,35–37] It is well absorbed orally, but its bioavailability is reduced substantially by first-pass metabolism in the liver.[38] The daily dosage of verapamil ranges from 240 to 480 mg administered in 3 to 4 doses. Total dosage as high as 720 mg/day has been used without adverse effects. Hemodynamic effects from oral verapamil are evident at 1 to 2 hours and the peak effect is 4 to 5 hours after its administration. The excretion of verapamil is primarily renal.

Adverse effects from verapamil administration may include marked bradycardia; AV block; peripheral vasodilation leading to hypotension, headache or dizziness; and reduced intestinal smooth muscle motility leading to constipation.[1,13,39–42] Thus, verapamil should be given with caution to the patient with sinus bradycardia, "sick sinus syndrome," AV block or left ventricular (LV) dysfunction. In addition, patients with LV failure or heart block should not receive concomitant therapy with β-adrenergic blockers or disopyramide, because this combination may cause profound heart failure or AV block. The overall incidence of adverse effects is 9 to 10%, but severe reactions requiring discontinuation of verapamil occur in only 1% of patients.[43]

Nifedipine is a potent vasodilator that is particularly effective in the treatment of patients with ischemic heart disease or systemic arterial hypertension.[3,44,45] In addition, it has been used as an unloading agent in patients with severe LV failure,[46] and it may reduce pulmonary arterial pressure and resistance in patients with pulmonary hypertension.[47,48] Unlike verapamil, nifedipine exerts no effect on cardiac conduction and, therefore, is not useful in the treatment of supraventricular tachyarrhythmias. Its absorption is nearly complete after oral or sublingual administration; the onset of action is within 20 minutes of an oral dose and within 5 minutes when given sublingually.[49] The duration of effect is 8 to 12 hours, and the usual oral dose is 10 to 40 mg every 6 to 8 hours; dosages up to 160 mg/day have been used safely. Its excretion is primarily renal.[49] Adverse effects, including headache, dizziness, flushing and dysesthesias, occur in up to 40% of patients but are sufficiently severe to require its discontinuation in only about 5%.[50,51]

Diltiazem is useful in patients with ischemic heart disease, and it may also be effective in those with supraventricular tachyarrhythmias.[52–54] Like verapamil, diltiazem impairs AV conduction and decreases the rate of sinus nodal impulse formation. Therefore, concomitant use with β-adrenergic blockers may be hazardous in the person with sinus bradycardia or conduction system disease. Diltiazem is well absorbed orally, with daily dosage of 180 to 360 mg administered in 3 to 4 doses. Its onset of action is within 30 minutes of its administration, and it has a plasma half-life of 4 hours.[55] In contrast to verapamil and nifedipine, its excretion is primarily hepatic. Adverse effects are uncommon and include headache, dizziness, flushing, gastrointestinal disturbances and skin rash.

Table I lists the clinical and pharmacologic considerations relevant to the administration of these 3 agents.

Clinical Applications

Prinzmetal's (variant) angina pectoris: Blinded and randomized comparisons of verapamil and placebo have demonstrated this calcium blocker's beneficial effect in decreasing the frequency of chest pain, nitroglycerin usage and episodes of transient ST-segment deviation (Fig. 6).[13,56–58] Similarly, nifedipine is efficacious in decreasing the frequency of pain in patients with this clinical problem.[50,59–61] In patients with this syndrome given open-label nifedipine (40 to 160 mg/day), the frequency of anginal episodes was markedly decreased, with a complete relief of angina in nearly two thirds and a diminution of anginal frequency by ≥50% in almost all patients.[50] Diltiazem has been evaluated in 2 blinded studies of 10 to 12 weeks' duration encompassing 25 patients with Prinzmetal's angina.[52,53] In comparison to placebo, diltiazem (240 mg/day) caused a significant decrease in the frequency of chest pain and nitroglycerin usage.

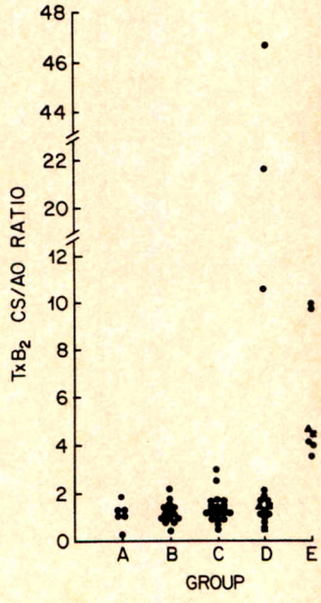

FIGURE 5. Ratios of coronary sinus (CS) to ascending aortic (AO) thromboxane B_2 (TxB_2) values in 5 groups of patients with various kinds of heart disease: group A (valvular and congenital nonischemic heart disease), group B (chest pain without ischemic heart disease), group C (ischemic heart disease without chest pain for >96 hours), group D (ischemic heart disease and chest pain within 24 to 96 hours of study) and group E (ischemic heart disease and chest pain within 24 hours of study). Those with continuing unstable angina (group E) have higher ($p < 0.05$) CS/AO TxB_2 ratios than other groups. Reproduced with permission from *N Engl J Med.*[16]

TABLE I Clinical Aspects of Calcium Antagonists

Drug	Dosage	Uses	Adverse Effects	Precautions
Verapamil	IV 0.075–0.150 mg/kg oral 80–120 mg every 6–8 hours	Supraventricular tachyarrhythmias Hypertrophic cardiomyopathy Variant angina pectoris Stable (exertional) angina Unstable angina at rest ? Protection of ischemic myocardium	Hypotension, headache, dizziness, pedal edema, constipation, AV nodal block	Use with β blockers may produce AV nodal block and/or LV dysfunction Use with disopyramide may cause LV dysfunction Use in digitalis excess or sick sinus syndrome may result in AV nodal block
Nifedipine	Oral or SI 10–40 mg every 6–8 hours	Systemic hypertension Variant angina pectoris Stable (exertional) angina Unstable angina at rest ? Protection of ischemic myocardium Unloading agent in patients with CHF Pulmonary hypertension	Hypotension, headache, flushing, pedal edema, dizziness	Use with β blockers generally safe Rarely may produce marked hypotension and increased angina
Diltiazem	Oral 30–90 mg every 6–8 hours	Stable (exertional) angina Variant angina pectoris ? Unstable angina at rest	Headache, dizziness, flushing, skin rash	Use with β blockers not evaluated but may result in AV nodal block or sinus bradycardia

AV = atrioventricular; CHF = congestive heart failure; IV = intravenous, LV = left ventricular; SI = sublingual.
Adapted from Winniford et al.[1]

There is little information concerning the relative efficacies of the slow-channel calcium antagonists in patients with Prinzmetal's angina. In 23 patients with this syndrome, we have shown that nifedipine and verapamil produce similar reductions in the frequency of chest pain, nitroglycerin usage, and ST-segment deviations (recorded by ambulatory electrocardiographic monitoring) (Fig. 7).[62] Studies from Japan suggest that nifedipine (30 to 60 mg/day) and diltiazem (90 to 240 mg/day) may be more effective than verapamil (120 to 320 mg/day) in treating variant angina, but these drugs were not compared directly in the same patients, and optimal doses of each were not administered.[63]

Unstable angina pectoris: The optimal medical therapy for the patient with unstable angina is controversial, but several studies have suggested that the slow-channel calcium antagonists may relieve angina in many of these patients.[64–70] In blinded, placebo-controlled evaluation, we and others have shown that verapamil significantly decreases the frequency of chest pain, nitroglycerin usage and ST-segment deviations (Fig. 8).[64,69] Other studies have shown that nifedipine (in doses of 40 to 80 mg/day) causes a significant decrease in anginal frequency when given to patients with continuing pain despite traditional antianginal therapy (Fig. 9).[70] However, Muller et al[71] have recently shown that nifedipine therapy alone is no better than conventional therapy in the treatment of patients with unstable angina pectoris. In a relatively small number of patients with unstable angina, diltiazem has been shown effective, especially in those whose angina is associated with transient ST-segment elevation.[68] Thus, the slow-channel calcium antagonists are efficacious in patients with unstable angina, particularly those in whom coronary arterial spasm is of etiologic importance.

Protection of ischemic myocardium: During prolonged ischemia and with acute myocardial infarction, the sarcolemmal membrane develops permeability defects to calcium that allow the intracellular calcium concentration to increase.[72–75] The development of these defects appears to correlate with loss of certain phospholipids from the sarcolemmal membrane and with structural defects in the sarcolemma.[72–75] In addition, sodium-calcium exchange may lead to cellular loading with calcium during both prolonged ischemia and temporary ischemia followed by reperfusion.[76] As the intracellular calcium concentration increases, the mitochondria sequester excessive amounts. As a result, mitochondrial oxidative phosphorylation is impaired, and less adenosine triphosphate (ATP) is available for normal metabolic processes, including maintenance of the structural integrity of the sarcolemmal membrane.[77] The entry of calcium into the myocardial cells also activates phospholipases capable of causing additional sarcolemmal damage and irreversible cellular injury.[77] Thus, irreversible cell injury during severe and prolonged myocardial ischemia and with myocardial infarction probably occurs because of structural and biochemical alterations to the sarcolemmal membrane that allow the loss of intracellular constituents and

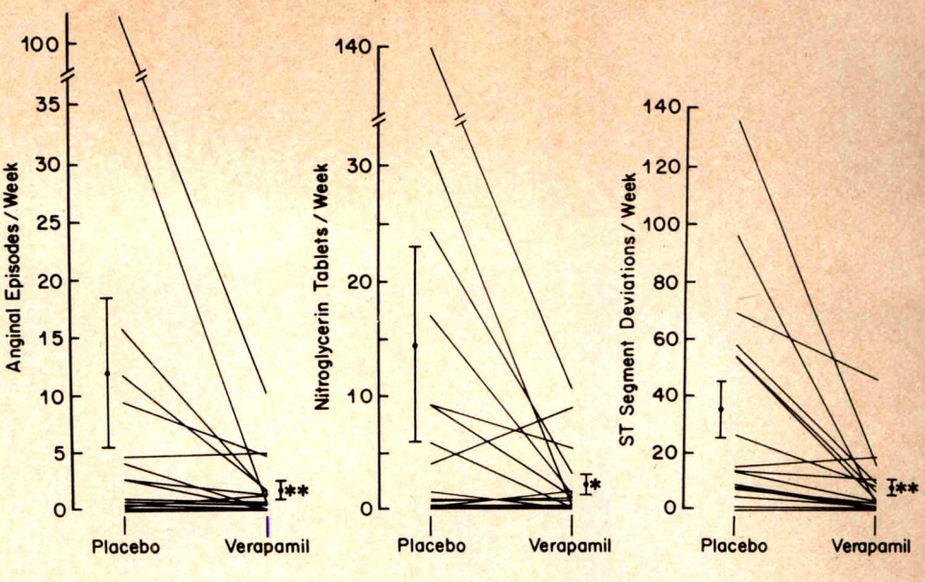

FIGURE 6. Number of anginal episodes per week (**left**), nitroglycerin tablets consumed per week (**middle**) and transient ST-segment deviations on calibrated 2-channel ambulatory electrocardiographic monitoring (**right**) in 16 patients with variant angina pectoris during therapy with placebo or verapamil. Each line represents data from 1 patient, and mean ± standard error of mean is shown on either side of each group of lines. Verapamil diminished all 3 variables ($p < 0.05$). Reproduced with permission from *N Engl J Med.*[13]

unrestricted entry of calcium and other usually extracellular ions. Whether the unrestricted entry of calcium intracellularly is a critical event in the development of irreversible cellular injury remains a controversial issue.

Because 1 route of transsarcolemmal calcium entry into the cell is through slow-calcium channels, pharmacologic antagonism of slow-channel calcium transport during myocardial ischemia may help to reduce the intracellular calcium concentration, thereby prolonging cell viability. However, this is probably effective only for brief periods of ischemia, because generalized alterations in membrane permeability and structural defects in sarcolemmal membranes occur with severe and prolonged ischemia and with myocardial infarction. Nevertheless, with short periods of myocardial ischemia, slow-channel calcium antagonists may help to protect injured myocytes by increasing coronary blood flow to the ischemically injured cells, by reducing myocardial oxygen demand and, potentially, by diminishing total cellular calcium burden in the injured cells.

In the experimental animal, nifedipine increases collateral perfusion of ischemic myocardium and reduces the extent of myocardial injury, particularly at sites that are only mildly injured.[78–80] Verapamil may reduce ischemic-induced contracture, mitochondrial calcium accumulation and infarct size.[81–83] Diltiazem decreases reperfusion-induced injury after temporary arterial occlusion and, in combination with propranolol, protects LV segmental function at moderately injured sites.[84–86] Thus, in the experimental animal, selected calcium antagonists given before or soon after short periods of coronary arterial occlusion or temporary coronary occlusion and reperfusion may protect segmental LV function and reduce the extent of myocardial injury. However, Urquhart et al[87] have demonstrated different potencies during acute myocardial ischemia in canine models for verapamil, diltiazem and nifedipine on LV function and heart rate when compared with their relative vasodilator capabilities.

It is not yet clear whether calcium antagonists possess the ability to reduce infarct size and preserve ventricular function during acute myocardial infarction associated with permanent or temporary coronary arterial occlusion followed by reperfusion in man. However, the initial evaluations of selected calcium antagonists administered during evolving myocardial infarction are not terribly encouraging.[88–90] In a double-blind, multicenter Norwegian study, 227 patients with suspected acute myocardial infarction received nifedipine or placebo within 12 hours of onset of symptoms.[88] Ni-

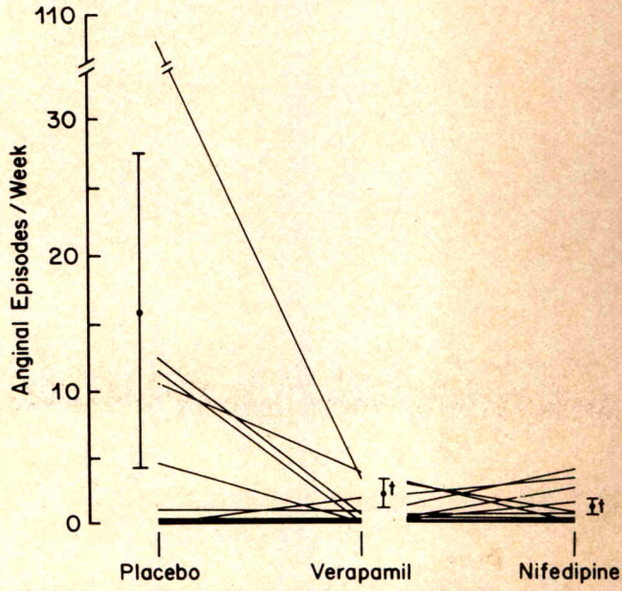

FIGURE 7. Number of anginal episodes per week during therapy with placebo (**left**), verapamil (**middle**) and nifedipine (**right**) in 10 patients with Prinzmetal's angina pectoris. Each line represents data from 1 patient, and mean ± standard error of mean is shown on either side of the lines. Compared with placebo, verapamil and nifedipine reduced frequency of angina. Reproduced with permission from *Am J Cardiol.*[62]

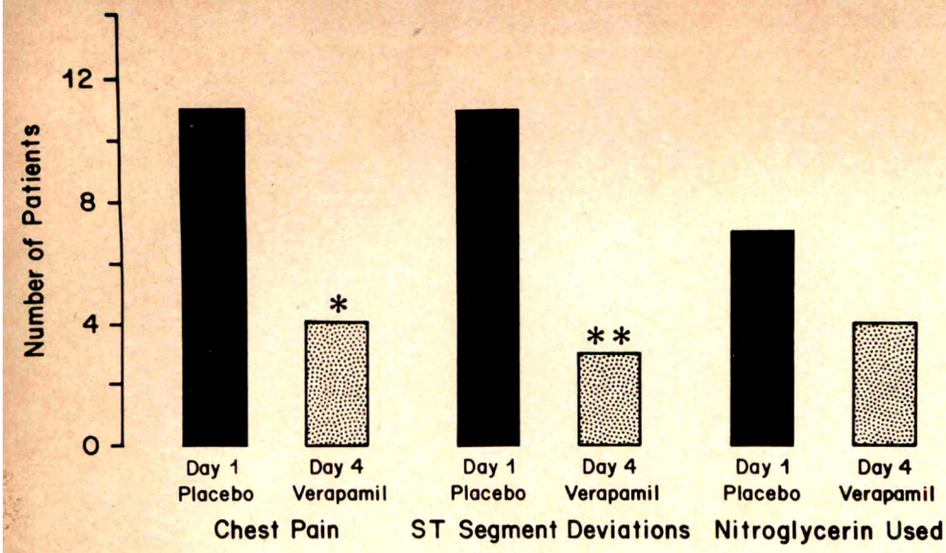

FIGURE 8. Number of patients with chest pain (**left**), ST-segment deviation (**middle**) and nitroglycerin usage (**right**) on day 1 (placebo) and day 4 (verapamil) in 11 patients hospitalized with severe unstable angina pectoris. Verapamil reduced chest pain and ST-segment deviation but not number of nitroglycerin tablets consumed. Four patients continued to have chest pain during verapamil therapy, and 3 patients continued to have transient ST-segment deviations. Reproduced with permission from *Am Heart J.*[69]

fedipine failed to reduce infarct size as measured by creatine kinase-MB (CK-MB) infarct size determinations.[88] Similarly, Muller et al[89] were unable to demonstrate that nifedipine reduced the frequency or size of acute myocardial infarction in a randomized study of 110 patients given either nifedipine (20 mg orally every 4 hours for 14 days) or placebo within a mean of 5.2 ± 2.5 (standard error) hours after the onset of chest pain. However, data from Bussman et al[90] suggest that intravenous verapamil given within 8 hours and continued for 2 days postmyocardial infarction may reduce infarct size, as measured by CK and CK-MB, by approximately 30% in patients. Each of these studies evaluated relatively small numbers of patients without reperfusion and relatively late after myocardial infarction. It remains to be determined conclusively whether a selected calcium antagonist may reduce infarct size and preserve ventricular function when given relatively early after the onset of symptoms or when administered during reperfusion associated with thrombolytic therapy or both.

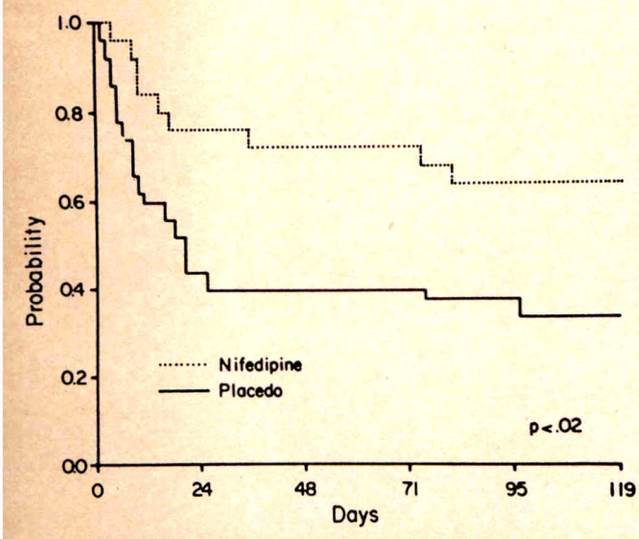

FIGURE 9. Effect of nifedipine on efficacy of medical therapy in patients with ST-segment elevation during unstable angina pectoris over a 119-day follow-up period. Compared with placebo, nifedipine significantly increased the likelihood that medical therapy was effective during this period of followup. Reproduced with permission from *N Engl J Med.*[70]

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Use of Nifedipine to Decrease Ischemic-Reperfusion Injury in the Surgical Setting

RICHARD E. CLARK, MD, IGNACIO Y. CHRISTLIEB, MD, JOHN C. VANDERWONDE, MD, and PHILIP D. HENRY, MD

This report summarizes studies that provided a basis for a randomized clinical trial of nifedipine in cold hyperkalemic cardioplegic solution. Data from normothermic, isolated working rabbit heart studies demonstrated that presence of micromolar concentrations of nifedipine in the perfusate during continuous low flow or nifedipine used as bolus washouts during global ischemia prevented increases in systolic and diastolic stiffness, which could be related to dose and prevention of intracellular accumulation of calcium. Other studies in open-chest dogs in whom regional ischemia was produced showed that nifedipine was superior to sodium nitroprusside when infused during the ischemic and reperfusion intervals with respect to preservation of hemodynamic variables and reduction of myocardial injury. Further, data from cardiopulmonary bypass experiments in dogs conducted at myocardial temperatures of 37, 28, 18 and 12°C with 1, 2 and 3 hours of global ischemia all demonstrated significant efficacy.

To date, the randomized clinical trial has shown a small reduction in the incidence of low cardiac output syndrome in high-risk patients. Those receiving nifedipine had improved hemodynamic variables. No patient in the treated group had myocardial injury in the postoperative interval shown by radionuclide pyrophosphate scan. The conclusions from this trial are that nifedipine was efficacious when included in a cold hyperkalemic cardioplegic solution. The responses observed, however, appear to be dose-, vehicle- and species-dependent.

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Chemical cardioplegia for preservation of ischemic myocardium during cardiac surgery has been in use for 25 years.[1] During this interval, a few basic principles for myocardial preservation have evolved. First, hypothermia is a potent protective agent.[2–7] Second, it is essential to prevent rapid degradation of high-energy phosphate compounds by immediate cessation of electrical and mechanical activity of the heart concomitant with the onset of global ischemia.[8–12] Third, the functional result obtained after ischemia and reperfusion is strongly related to the preischemic biochemical and morphologic status of the heart and the duration and temperature during the ischemic period.[13–16] Fourth, during the initial minutes of the reperfusion period, the myocardium is highly susceptible to further injury, but the mechanisms governing further injury or recovery during this interval are incompletely understood.[17–20] Finally, the chemical composition of the solution, the frequency and volume administered and the rate of delivery are highly important to the degree of preservation achieved.[13,21–26]

Early in the ischemic process, an increase in intracellular calcium (Ca^{++}) concentration results in inappropriate activation and impairment of synthesis of adenosine triphosphate. There is an accelerated depletion of high energy stores paralleled by impaired myocardial relaxation. During the initial reperfusion phase, flooding of the cell by Ca^{++} may occur and lead to myocardial rigor, a state that has been termed the "stone heart." Myocardial reperfusion after temporary ischemia[27] or perfusion with Ca^{++}-free perfusate[28] has been reported to result in accumulations of intracellular Ca^{++} and in explosive deteriorations in myocardial structure and function. Calcium deposits have also been described in the cardiac lesions produced by the administration of large amounts of catecholamines[29] and in the cardiomyopathy of the Syrian hamster.[30]

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Address for reprints: Richard E. Clark, MD, Surgery Branch, National Heart, Lung, and Blood Institute, Building 10, Room 2N242, National Institutes of Health, Bethesda, Maryland 20205.

Fleckenstein[31] and collaborators were the first to delineate a group of compounds they referred to as Ca^{++} antagonists, which inhibited the contractile activity of cardiac and smooth muscle by blocking the inward movement of Ca^{++} into cells. Fleckenstein[29] further demonstrated that pretreatment with the Ca^{++} antagonists verapamil and D-600 protected rats from catecholamine-induced cardiac necrosis and Ca^{++} accumulation and Syrian hamsters from the development of their genetically determined cardiomyopathy.

The studies summarized herein covered a 7-year period[32–40] and provided the basis for the initiation of a clinical trial of nifedipine in cardioplegic solution. The rationale was that prevention of the abnormal accumulation of intracellular Ca^{++} during ischemia and reperfusion could be ameliorated with the use of a Ca^{++} antagonist, which would result in less of a depletion of high-energy phosphate stores, less of an increase in stiffness and less of a decrease in contractility. We chose nifedipine because previous studies demonstrated it has the potential to exert protective effects on the myocardium.[18,32,33]

Normothermic Isolated Perfused Heart Preparation—Low Flow Studies

Rabbit hearts were isolated and perfused retrograde at 37°C through the aorta as previously described.[9] The perfusate was a modified Krebs-Henseleit solution equilibrated with a 5% carbon dioxide-95% oxygen gas mixture. The pH was approximately 7.4. The rate of perfusion was maintained at 22 ml/min with a roller pump. A latex balloon mounted around a micromanometer (Konigsberg model P3.5) was inserted into the left ventricular (LV) cavity for measurement of LV pressure and its first-time derivative (dP/dt). The heart was paced at 180 beats/min. The major determinants of cardiac performance were controlled. All hearts were equilibrated for 30 minutes at a flow rate of 22 ml/min. Then, slow perfusion (0.2 ml/min; 5 ml/100 g fresh myocardium/min) with perfusate containing nifedipine or its vehicle was started and maintained for 60 minutes. The drug, or its vehicle in control experiments, was infused with a syringe pump into the perfusion system at a rate not exceeding 1% of the total flow. In some experiments, high flow (22 ml/min) without nifedipine was reinstituted (reperfusion) at the end of the slow flow interval. In other experiments, hearts at the end of perfusion were used to determine the ventricular wet weight/dry weight ratio. The Ca^{++} content of the mitochondrial fraction was assayed and used as an index of cell Ca^{++}. This approach is based on the finding, which has been described in detail previously,[18] that most of the Ca^{++} accumulating in ischemic myocardium is recovered in the mitochondria and mitochondrial cristae.

A representative record of an isovolumic left-side heart preparation subjected to 60 minutes of low flow (0.2 ml/min) is illustrated in Figure 1, top panel. Once ischemic standstill had occurred, the ventricle had progressive ischemic contracture. Ventricular pressure at the end of the ischemic period exceeded 50 mm Hg. With subsequent reperfusion, end-diastolic pressure remained markedly increased, which indicated persistent myocardial stiffness. In addition, the heart was arrhythmic despite ventricular pacing. Figure 1, bottom, shows the response of a heart subjected to exactly the same protocol except that nifedipine (10^{-7} M) was added to the perfusate during (but not before or after) low flow. As in the control experiment, there was a precipitous decrease in cardiac contractility followed by ventricular standstill. However, in sharp contrast to the control experiments, no contracture developed. Furthermore, with reperfusion, end-diastolic pressure (EDP) remained low, and there was a striking recovery

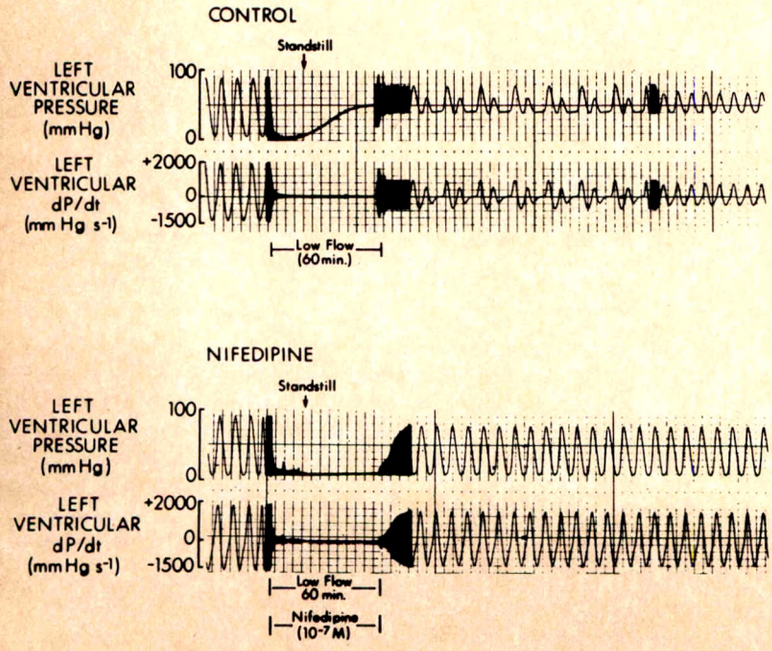

FIGURE 1. Inhibition of ischemic ventricular contracture by nifedipine. Perfusion experiments with paced isovolumic left heart preparations were performed as described in the text. Standstill refers to no visible ventricular activity and no pulsatile pressure on tracings recorded with a second recorder at paper speed of 25 mm/s and full scale of 100 mm Hg. Low flow refers to rate of perfusion of 0.2 ml/min. Fast and slow (**black areas**) segments of tracings were recorded at paper speed of 25 mm/s and 1 mm/min, respectively. dP/dt = first derivative of left ventricular pressure. Reprinted with permission from Raven Press. In: Winbury MM, Abiko Y, Eds. *Ischemic Myocardium and Antianginal Drugs*. New York: Raven Press, 1979.

in developed pressure and dP/dt. Results of the experiments depicted in Figure 1 are diagrammatically summarized in Figures 2 and 3. Results of measurements of calcium, copper and protein in perfused hearts and in hearts processed immediately after sacrifice of the animal are summarized in Table I. Perfusion at high flow resulted in only a minor increase in mitochondrial Ca^{++}. Sixty minutes of low flow without nifedipine increased the Ca^{++} value more than 4-fold, and subsequent reperfusion for 10 minutes produced a further marked increase. In contrast, in nifedipine-treated hearts subjected to low flow with or without reperfusion, accumulation of Ca^{++} in the mitochondrial fraction remained modest.

Figure 4 shows the relation between myocardial stiffness, as reflected by the nonpulsatile ventricular pressure at the end of the low-flow period (contracture pressure) or by the EDP after 10 minutes of reperfusion, and accumulation of Ca^{++} in the mitochondrial fraction. Increasing myocardial stiffness was associated with increasing Ca^{++} values, and reperfusion enhanced the accumulation of Ca^{++}. Treatment with nifedipine prevented ischemic myocardial stiffness as well as Ca^{++} accumulation.

Global Ischemia in an Isolated Heart Preparation: Determination of Dose-Response Relations

The empiric addition of agents to cardioplegic solutions may be harmful at certain concentrations and beneficial at others. We conducted the following experiments to develop a stable, isolated heart preparation of global ischemia with which to assess dose-response relations of calcium-channel blockers. The preparation was designed to allow measurement of both LV pres-

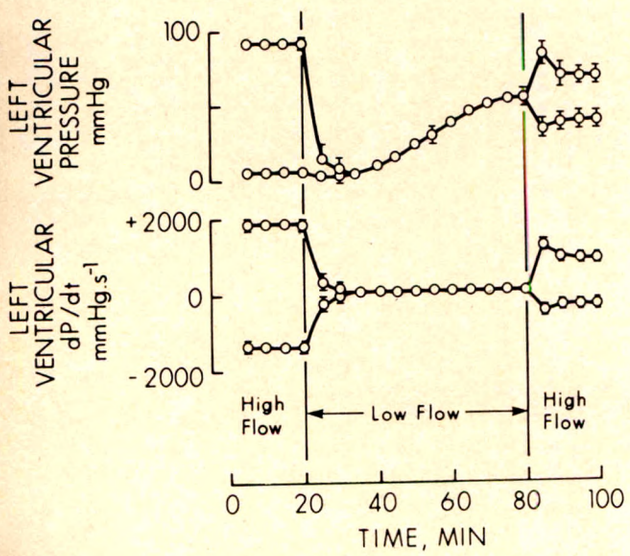

FIGURE 2. Ischemic contracture in isovolumic left heart preparations (n = 8). Perfusions were performed as described in the text and illustrated in Figure 1, top. High and low flow refer to flow of 22 and 0.2 ml/min, respectively. Buffer during low flow contained <0.1% of the vehicle of nifedipine (final ethanol and polyethylene glycol concentrations both <0.015%). Data points indicate mean ± standard error. dP/dt = first derivative of left ventricular pressure. Reprinted with permission from Raven Press. In: Winbury MM, Abiko Y, Eds. *Ischemic Myocardium and Antianginal Drugs*. New York: Raven Press, 1979.

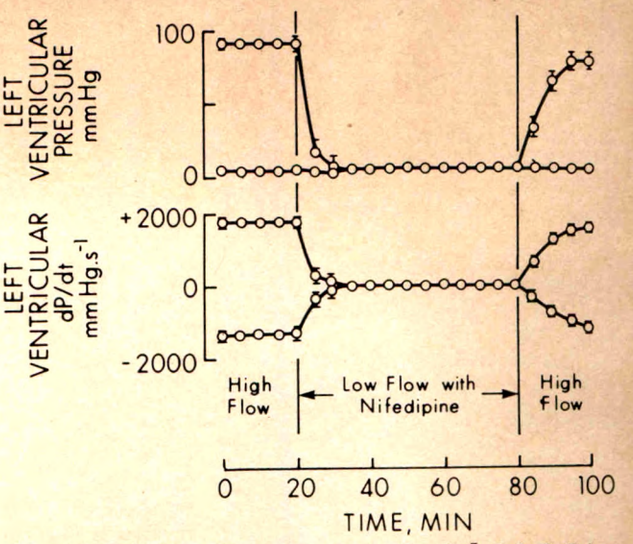

FIGURE 3. Inhibition of ischemic contracture by 10^{-7} *M* of nifedipine (n = 8). Experiments were performed exactly as described in the text and illustrated in Figure 1, except that the vehicle contained nifedipine to yield final drug concentration of 10^{-7} *M*. No nifedipine was administered before or after period of low flow. Data points indicate mean ± standard error. Reprinted with permission from Raven Press. In: Winbury MM, Abiko Y, Eds. *Ischemic Myocardium and Antianginal Drugs*. New York: Raven Press, 1979.

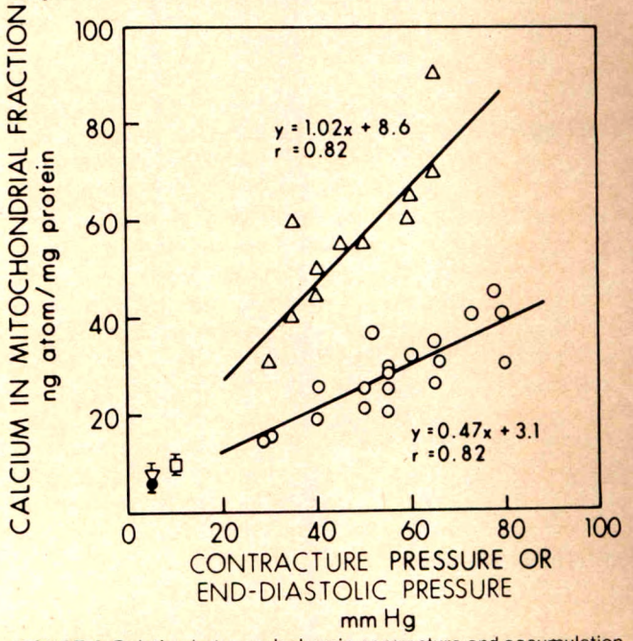

FIGURE 4. Relation between ischemic contracture and accumulation of calcium in the mitochondrial fraction. Perfusions were performed as described in the text. Mitochondrial fractions were prepared with solutions containing ruthenium red. **Solid circle with bars:** after a standard equilibration period, hearts were perfused at 22 ml/min for 60 minutes with buffer containing no nifedipine (n = 7). **Open inverted triangle with bars:** perfusions at low flow (0.2 ml/min) for 60 minutes with buffer containing nifedipine (10^{-7} *M*) and its vehicle (n = 9). **Open square with bars:** after a 60-minute period of low flow with nifedipine, hearts were reperfused at 22 ml/min for 10 minutes with buffer containing no nifedipine (n = 10). **Open circles:** 60-minute perfusions at low flow with buffer containing vehicle without nifedipine. **Open triangles:** 60 minutes of low flow with buffer containing vehicle without nifedipine, followed by 10 minutes of reperfusion. Data points represent mean ± standard error and are from the same experiments as summarized in Figures 2 and 3 and Table I. Reprinted with permission from Raven Press. In: Winbury MM, Abiko Y, Eds. *Ischemic Myocardium and Antianginal Drugs*. New York: Raven Press, 1979.

TABLE I Calcium and Copper in Mitochondrial Fraction*

	Hearts (n)	Calcium ng atom (mg protein)	Copper ng atom (mg protein)	Calcium/ Copper	Copper in mitochondrial fraction (%)	Protein in mitochondrial fraction (%)
No perfusion†						
−N	8	6.2 ± 0.3	1.37 ± 0.05	4.53 ± 0.23	10.9 ± 0.4	4.01 ± 0.22
+N	8	6.3 ± 0.3	1.36 ± 0.06	4.63 ± 0.24	11.4 ± 0.5	4.12 ± 0.23
−R	7	6.8 ± 0.4	1.38 ± 0.04	4.93 ± 0.29	10.7 ± 0.4	4.10 ± 0.19
60 minutes high flow‡						
−N	7	7.6 ± 0.4	1.38 ± 0.06	5.51 ± 0.41	11.6 ± 0.5	4.21 ± 0.25
+N	8	7.4 ± 0.4	1.34 ± 0.06	5.52 ± 0.43	12.0 ± 0.7	4.05 ± 0.28
60 minutes low flow§						
−N	10	28.2 ± 1.9	1.41 ± 0.05	19.9 ± 1.61	9.2 ± 0.9	3.41 ± 0.21
+N	10	8.0 ± 0.5	1.30 ± 0.07	6.15 ± 0.55	10.8 ± 0.7	4.15 ± 0.27
60 minutes low flow + 10 minutes reperfusion‖						
−N	11	55.5 ± 4.8	1.29 ± 0.09	42.65 ± 3.9	6.8 ± 0.7	2.52 ± 0.21
+N	12	10.0 ± 0.6	1.33 ± 0.10	7.52 ± 0.63	9.4 ± 0.7	3.50 ± 0.24
−R	9	58.6 ± 6.0	1.31 ± 0.12	44.73 ± 4.8	6.2 ± 0.8	2.31 ± 0.30

* Percentages of copper or protein in the mitochondrial fraction are expressed as percentages of the total myocardial copper or protein in the whole homogenate. Values are mean ± standard error.

† No perfusion: hearts processed immediately after killing the animal without Langendorff perfusion; in these preparations, −N and +N refer to the absence or presence, respectively, of 10^{-7} *M* nifedipine in the preparative solutions, and −R indicates that ruthenium red was omitted from all preparative solutions.

‡ High flow: perfusion at 22 ml/min; in perfused hearts, −N and +N refer to the addition of vehicle alone or vehicle plus nifedipine (10^{-7} *M*), respectively, to the perfusate during the experimental perfusion period (60 minutes).

§ Low flow: perfusion at 0.2 ml/min; −N and +N as in high flow.

‖ Reperfusion: −R indicates that perfusion was carried out without nifedipine and that ruthenium red was omitted from all preparative solutions; −N and +N, as in high flow and low flow. Reprinted with permission from Raven Press. In: Winbury MM, Abiko Y, Eds. *Ischemic Myocardium and Antianginal Drugs*. New York: Raven Press, 1979.

sures and flow without an apex puncture or use of an isovolemic balloon. The use of rabbit hearts served a 2-fold purpose: avoidance of an excessive number of costly canine experiments in the initial screening for dose responses and avoidance of the rat heart, given its known species-specific resistance to digitalis glycosides and other anomalous cardiac responses.

Dual perfusion circuits and hearts (over 230) isolated from New Zealand White rabbits (2.5 ± 0.3 kg) were used. After intravenous heparin (500 μ/kg) and pentobarbital (60 mg/kg) anesthesia, hearts were excised and mounted on an isolated working heart apparatus. A unique dual lumen-left atrial cannula provided access for anterograde flow and high-fidelity measurement of LVEDP and positive and negative dP/dt. At constant heart rate and mean aortic pressures, LV function curves were developed relating stroke work indexes (SWIs) to LVEDP. Coronary flow indexes per gram of heart weight, myocardial oxygen consumption ($M\dot{V}O_2$) and developed LV pressure were measured as the function curves were generated. One hundred hearts were perfused in development of the technique. A Krebs-Henseleit albumin perfusate allowed 3 hours of continuous work with minimal deterioration (Control group C-1). Two additional control groups (C-2 and C-3) and 2 cardioplegic solution groups (cardioplegic solutions and cardioplegic solutions + nifedipine) were studied at 38 ± 0.5°C. Group C-2 (n = 17) was given rapid volume loading at 5 and 115 minutes of perfusion to assess performance as a function of time. Group C-3 (n = 10) was given 30 minutes of global ischemia and reperfusion to assess effects of unaltered ischemia on the preparation. Hearts given cardioplegic solution (n = 32) and cardioplegic solutions + nifedipine (n = 12) had two 10-ml aortic root injections of cardioplegic solutions (potassium = 27 m*M*) at 0 and 15 minutes of global ischemia. Nifedipine was added to cardioplegic solutions in a concentration found effective in dog and man (0.2 μg/ml). In other studies (n = 25), nifedipine was added in doses of 0.01 to 0.40 μg/ml to define dose-response relations. Data were analyzed by analysis of variance.

The results of groups of C-2, C-3, cardioplegic solutions and cardioplegic solutions + nifedipine are summarized in Table II. This preparation had stable SWI and $M\dot{V}O_2$ and negative dP/dt over 2 hours of perfusion (difference is not significant [p = NS]) with time-related degradation of coronary flow indexes, positive dP/dt and developed LV pressure (all $p < 0.001$) to a level of 90 to 95% of preischemic values. In group, C-3, 30 minutes of unaltered global ischemia resulted in ischemic contracture in 60% of the hearts. In groups given cardioplegic solutions, all measurements of cardiac function were decreased from preischemic values ($p < 0.001$). The addition of nifedipine produced an amelioration of decreased function.

Whereas cardioplegic solutions without nifedipine resulted in a 45% decrease in SWI, the addition of nifedipine yielded a 17% decrease ($p < 0.05$) and $M\dot{V}O_2$ was equal to the preischemic value. Further, there was marked improvement in the postischemic coronary flow indexes ($p \leq 0.01$) and negative dP/dt ($p \leq 0.05$). Doses of nifedipine <0.10 μg/ml were not effective and doses of >0.4 μg/ml were harmful.

Regional Ischemia in Open-Chest Dogs

One hundred twelve mongrel dogs were anesthetized, intubated and ventilated, and had left thoracotomies. Phasic and mean pressures were recorded through

TABLE II Results of Isolated Working Rabbit Heart Studies

Group	LVEDP (mm Hg)	SWI (g·m/dry g)	CFI (ml/min/dry g)	O_2Con (ml/min/dry g)	+dP/dt (mm Hg·s^{-1})	−dP/dt (mm Hg·s^{-1})	DLVP (mm Hg)
Before GI (n = 71)	0	0.70 ± 0.03	60 ± 2	0.61 ± 0.03	1,696 ± 61	1,484 ± 50	85 ± 2
	3	1.30 ± 0.03	69 ± 2	0.78 ± 0.02	1,912 ± 80	1,518 ± 43	92 ± 2
Group C-2	0	0.68 ± 0.02	57 ± 2	0.56 ± 0.03	1,665 ± 69	1,476 ± 46	83 ± 2
at 115 min of continuous perfusion (n = 17)	3	1.25 ± 0.03	62 ± 2	0.75 ± 0.03	1,813 ± 48	1,440 ± 34	88 ± 2
Group C-3 after unaltered GI (n = 10)	0	0	...	...	0	0	0
	3	0	...	...	0	0	0
		No heart recovered anterograde flow					
Group CPS	0	0.43 ± 0.03	54 ± 1	0.57 ± 0.02	1,492 ± 45	1,358 ± 39	73 ± 1
after GI (n = 12)	3	0.72 ± 0.06	57 ± 2	0.63 ± 0.02	1,601 ± 58	1,450 ± 58	79 ± 2
Group CPS + N	0	0.61 ± 0.04	58 ± 2	0.66 ± 0.03	1,594 ± 77	1,461 ± 66	76 ± 2
after GI (n = 12)	3	1.08 ± 0.06	64 ± 2	0.72 ± 0.02	1,733 ± 94	1,500 ± 66	81 ± 3

Values are mean ± standard error of the mean.
CFI = coronary flow index; CPS = cardioplegic solution; CPS + N = cardioplegic solution plus nifedipine; DLVP = developed left ventricular pressure; +dP/dt = positive first derivative of left ventricular pressure; −dP/dt = negative first derivative of left ventricular pressure; GI = global ischemia; LVEDP = left ventricular end-diastolic pressure; O_2Con = oxygen consumption; SWI = stroke work index.

catheters placed in the right atrium, ascending aorta, left atrium and left ventricle. An electromagnetic flow probe was applied to the ascending aorta for determination of plastic and mean flows. The LV pressure was differentiated and recorded directly as dP/dt. Occlusion of the left anterior descending coronary artery was accomplished with fine silicone rubber tubing. Animals were treated with aortic root infusions during the ischemic period of 1 or 2 hours duration, during the 2-hour reperfusion period (which was constant for all animals) or during both periods. Each animal had an infusion of either saline solution or saline solution plus sodium nitroprusside or nifedipine at a rate of 40 ml/h through an aortic root needle controlled by an infusion pump. The solutions were at room temperature and the dosage of nifedipine was 5 μg/kg/hour at an average concentration of 3 mg/ml or nitroprusside 3 μg/kg/min. These dosages resulted in similar decreases in blood pressure. Infusions were begun simultaneously with occlusion or release of the left anterior descending coronary artery. After 120 minutes of reperfusion, 100 mg/kg of colloidal carbon was injected through the left atrial catheter. After 5 minutes the heart was flushed and fixed in situ. The heart was cut with a calibrated slicer in slices approximately 5 mm thick, perpendicular to the apical-aortic root axis. After complete fixation, each slice was photographed and the volume of the ischemic-reperfusion injury determined morphometrically; the results were expressed as a percentage of total volume.

The use of nifedipine during ischemia only or during the reperfusion interval was associated with marked improvements in SWI, dP/dt and cardiac index compared with animals given the same volume of saline solution or saline solution containing nitroprusside. The comparisons for 1 and 2 hours of regional ischemia are summarized in Tables III and IV. Nifedipine was most efficacious when given during both time intervals and it maintained SWI and dP/dt at control levels with little change in LVEDPs. In the 1- and 2-hour ischemic experiments, there was a 2- and 3-fold decrease in injury volume, respectively. The changes noted were significantly different from the saline solution-treated and the nitroprusside-treated animals ($p \leq 0.01$).

Global Ischemia Using Cardiopulmonary Bypass

Normothermic experiments: Mongrel dogs were anesthetized and placed on a volume-limited ventilator. After a right lateral thoracotomy, catheters and flow transducers were placed, as previously described. A metal cannula was inserted into a common femoral artery for perfusion from the heart-lung machine. Venous drainage cannulas were inserted through the azygos vein into the superior vena cava and through the right atrial appendage into the inferior vena cava. Rectal, myocardial and blood temperatures were measured with thermistors. Before cannulation of the vena cavae, each animal was given 500 to 600 ml of filtered citrate phosphate-dextrose preserved (≤24 hours) canine whole blood in rapid sequential 50 ml aliquots and LV function curve was characterized. Three- to 5-minute intervals were utilized for each measurement before bypass. After the initiation of partial cardiopulmonary bypass, an LV vent was inserted through the right superior pulmonary vein. The perfusate was maintained at a temperature of 37.5 ± 0.5°C. A 14-gauge plastic cannula was placed in the aortic root proximal to the flow transducer for infusion of various perfusate solutions to be described later.

After adjustment of the extra- and intracorporeal blood volumes with the animal on partial cardiopulmonary bypass, a clamp was applied to the ascending aorta and the heart was rendered ischemic. Simultaneously, an infusion of room temperature (23 to 27°C) solution at 4 ml/min was begun into the root of the aorta. In other experiments, bolus injections of 150 to 200 ml at 37°C or room temperature were made in 90 seconds and repeated every 30 minutes. Total body perfusion was maintained at a minimal flow rate of 100 ml/kg/min at a minimal mean aortic pressure of 70 mm Hg. No drugs were administered during perfusion. Crystalloid and colloid volume were added as required to meet the prescribed hemodynamic criteria.

After 1 hour of normothermic myocardial ischemia, the clamp on the ascending aorta was removed and the hearts were reperfused for 30 minutes under steady-state flow and pressure conditions. If necessary, the heart was then defibrillated. Attempts were made to

TABLE III After 1 Hour of Ischemia and 2 Hours of Reperfusion

	Preischemia Normal Values (n = 25)	No Rx (n = 9)	Nitroprusside Rx Ischemia and Reperfusion (n = 8)	Nifedipine Rx Ischemia and Reperfusion (n = 8)
Stroke work index ($g \cdot m \cdot m^{-2}$)	19.7 ± 1.8	9.6 ± 1.6	12.7 ± 1.7	19.1 ± 1.6
dP/dt (mm $Hg \cdot s^{-1}$)	3,037 ± 139	2,294 ± 93	2,406 ± 205	3,125 ± 288
LVEDP (mm Hg)	11.3 ± 2.4	13.6 ± 2.8	12.5 ± 3.1	12.5 ± 1.5
Percent injury volume		4.8 ± 0.9	4.1 ± 0.9	2.0 ± 1.1

Rx = therapy. Other abbreviations as in Table II. Reprinted with permission from *Ann Surg.*[39]

TABLE IV After 2 Hours of Ischemia and 2 Hours of Reperfusion

	Preischemia Normal Values (n = 22)	No Rx (n = 7)	Nitroprusside Rx Ischemia and Reperfusion (n = 8)	Nifedipine Rx Ischemia and Reperfusion (n = 7)
Stroke work index ($g \cdot m \cdot m^{-2}$)	20.3 ± 1.3	10.6 ± 1.4	9.5 ± 1.5	18.0 ± 2.6
dP/dt (mm $Hg \cdot s^{-1}$)	3,161 ± 281	1,571 ± 298	2,063 ± 240	3,164 ± 276
LVEDP (mm Hg)	6.6 ± 1.7	13.9 ± 2.2	11.5 ± 2.0	10.1 ± 2.7
Percent injury volume		8.9 ± 1.9	6.2 ± 1.7	3.1 ± 0.8

Abbreviations as in Tables II and III. Reprinted with permission from *Ann Surg.*[39]

wean the animal from the extracorporeal circuit as quickly as possible. Blood volume was adjusted by infusion or withdrawal to maximize cardiac output. Once perfusion was discontinued, volume was added only when required to maintain a mean left atrial pressure similar to the average preischemic value. The animals were then observed for 2 hours without pharmacologic intervention.

Ventricular function was assessed by a comparison of variables measured directly and calculation of stroke volume, SWI and total peripheral resistance.

Hemodynamic data were evaluated statistically by both the paired and unpaired Student *t* tests. Each animal served as its own control for comparison of the preischemic and postischemic data (paired analysis). Preoperative and postoperative values for controls and experimental groups were compared by unpaired *t* test analysis. Pathologic studies were performed in a manner similar to that used for the regional ischemic experiments.

Solutions evaluated during normothermic global ischemic experiments: Three control solutions were used in 24 experiments: normal saline solution, normal saline solution with 25 mEq/liter of potassium chloride and Normosol®-pH 7.4. The first was used to study the influence of washout (continuous and intermittent) with

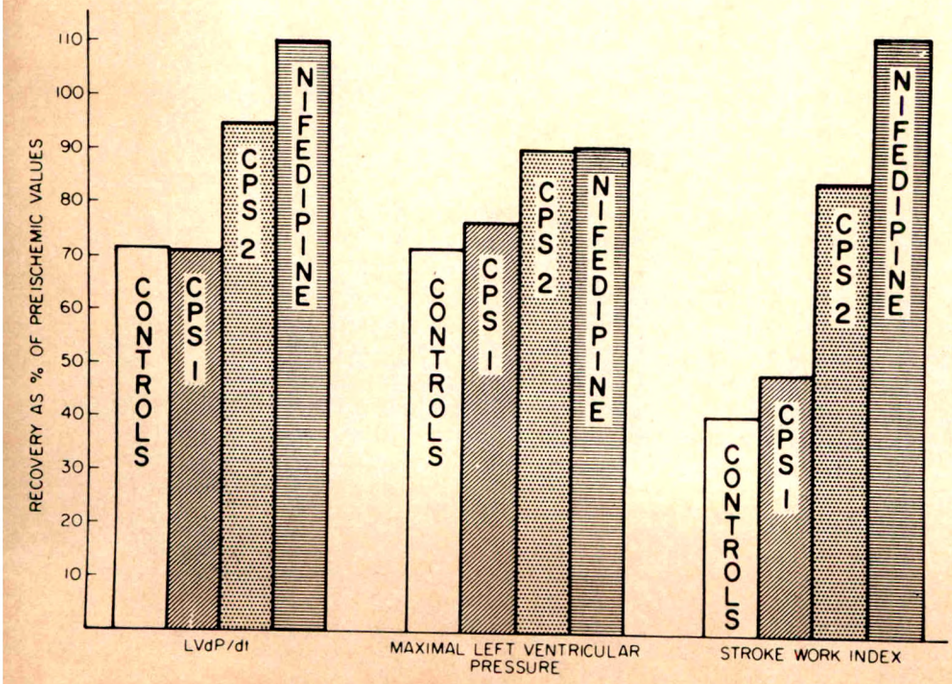

FIGURE 5. Recovery as a percentage of preischemic values is shown for left ventricular (LV) dP/dt, maximal LV pressure and stroke work index for groups of dogs given 1 hour of global ischemia at 37°C and treated with multiple doses of control solutions and extracellular-like cardioplegic solution (CPS 1) and intracellular-like cardioplegic solution (CPS 2) and saline and cardioplegic solutions containing 0.2 μg/ml of nifedipine (see Table IV for complete listing of hemodynamic variables). Reprinted with permission from *Ann Surg.*[39]

TABLE V Comparison of 2-Hour Postbypass Values* for Bolus Aortic Root Injections During 1 Hour of Normothermic Ischemia

Variable	Controls (n = 6)	CPS I—Extracellular Cardioplegic Solution (n = 8)	CPS II—Intracellular Cardioplegic Solution (n = 7)	Nifedipine (n = 9)	Statistical Comparison Comment
Heart rate (beats/min)	192 ± 17	161 ± 7	152 ± 7	151 ± 5	NS between treatment groups—all treatment groups versus controls, p <0.01
dP/dt (mm Hg·s^{-1})	4,000 ± 531	3,143 ± 406	3,485 ± 257	4,386 ± 240	Nifedipine versus CPS I & II, p <0.05
MLAP (mm Hg)	8.5 ± 1.0	7.5 ± 1.6	13.5 ± 2.2	4.9 ± 1.0	CPS II versus all groups, p <0.05–0.01
LVP-MAX (mm Hg)	129 ± 19	112 ± 12	125 ± 8	140 ± 4	Nifedipine versus CPS I, p <0.05
LVEDP (mm Hg)	10.5 ± 3.3	7.5 ± 1.1	9 ± 1.5	6.4 ± 1.5	p = NS for comparison of all groups
Cardiac output (liters/min)	2,220 ± 220	2,450 ± 325	2,160 ± 340	3,217 ± 184	Nifedipine versus controls, CPS I & CPS II, p <0.05–0.01
Stroke work index (g·m·m^{-2})	10.4 ± 1.9	14.0 ± 3.6	19.1 ± 2.7	25.7 ± 1.7	Nifedipine versus all groups, p <0.05–0.01
TPR (dynes s cm^{-5})	2,171 ± 321	2,196 ± 381	3,063 ± 296	2,273 ± 251	CPS II versus all other groups, p <0.05

* Mean ± standard error.
dP/dt = first derivative of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVP-MAX = maximum left ventricular pressure; MLAP = mean left atrial pressure; NS = not significant; TPR = total peripheral resistance.
For explanation of CPS I and CPS II, refer to text.

an isotonic pharmacologically inactive solution. The second was used as a control for the elevated potassium ion concentrations used in the 2 cardioplegic solutions tested. The third control solution was used because it was the base for 1 of the cardioplegic solutions and had a neutral pH in contrast to isotonic saline solution.

Two cardioplegic solutions were used in 31 experiments; one was an extracellular type and the second an intracellular type solution. Both had similar pH (7.7 to 7.8), osmolarity (340 to 360 mOsm/liter) and concentrations of potassium chloride, magnesium and lidocaine (25 mEq/liter, 3 mEq/liter and 250 mg/liter, respectively). The principal differences were in sodium ion concentrations (142 versus 28 mEq/liter), calcium (0 versus 0.6 mEq/liter), chloride (103 versus 28 mEq/liter) and substitution of Tham for sodium bicarbonate.

Nifedipine (0.167 to 0.20 μg/ml) was used in saline solution and in each of the 2 cardioplegic solutions in 23 experiments. Continuous infusions at 4 ml/min were tested in 48 experiments; multiple doses, given at a rate of 100 to 130 ml/min and a pressure of 90/100 mm Hg in the aortic root, were used in 30 studies.

The data for the various solution groups are summarized in Table V and Figure 5. At similar left atrial pressures and heart rates, the nifedipine-treated animals had greater LV stroke work indexes immediately after bypass than the cardioplegic-solution treated groups, which improved until the preischemic values were reached 2 hours after cessation of cardiopulmonary bypass (Fig. 6).

The differences in the functional capacity of the postischemic ventricle treated during ischemia with various solutions are demonstrated in Figure 7. Only those animals treated with the calcium antagonist responded in a normal manner to 50-ml incremental colloid volume infusions of 500 to 600 ml.

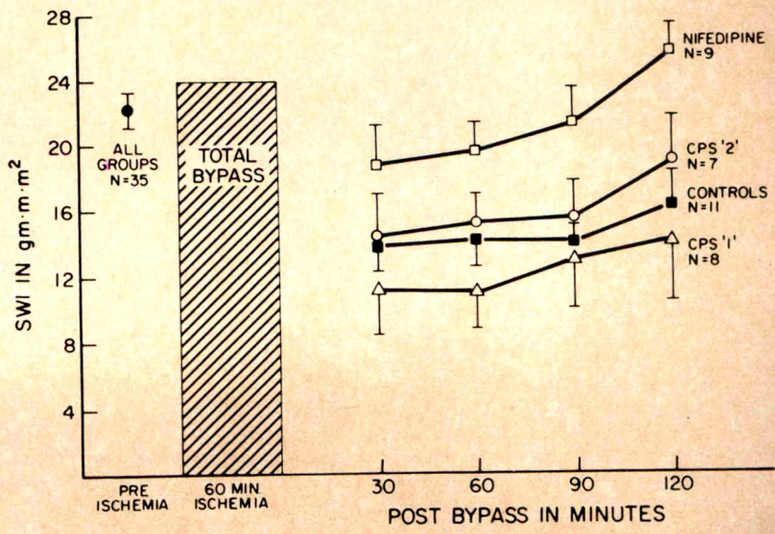

FIGURE 6. Stroke work index (SWI) versus event and time after bypass for 4 groups of dogs given 1 hour of global ischemia at 37°C and treated with multiple doses of control, 2 cardioplegic solution (CPS) and nifedipine solution. Reprinted with permission from *Ann Surg.*[39]

These data are for the bolus injection groups. The continuous infusion experiments demonstrated similar results, but recovery to preischemic levels was less in each subset than with the multidose mode of aortic root infusion.

Hypothermic experiments—1 or 2 hours of ischemia: Similar methods to those in the normothermic studies were used, with the following exceptions: 19 animals had global ischemia at 28°C for 1 hour (n = 5) and 2 hours (n = 14), and 24 dogs had global ischemia at an average myocardial temperature of 18°C for 1 hour (n = 6) and 2 hours (n = 18). The purpose of these studies was to ascertain the influence of 2 hypothermic myocardial temperatures frequently used in the clinical setting with 1 and 2 hours of ischemia on the degree of preservation conferred by control, cardioplegic and nifedipine solutions when given in multiple doses of 250 to 500 ml every 30 minutes. Solutions were at room temperature (30 ± 2°C) for the 28°C studies and 4°C for the 18°C studies. The solutions evaluated were control solutions of saline solution and Ringer's injection, the intracellular-like solution listed earlier, Ringer's injection containing 250 mg/liter of lidocaine, 27 mEq/liter of sodium bicarbonate and 25 mEq/liter of potassium chloride, and solution C containing 200 μg/liter of nifedipine.

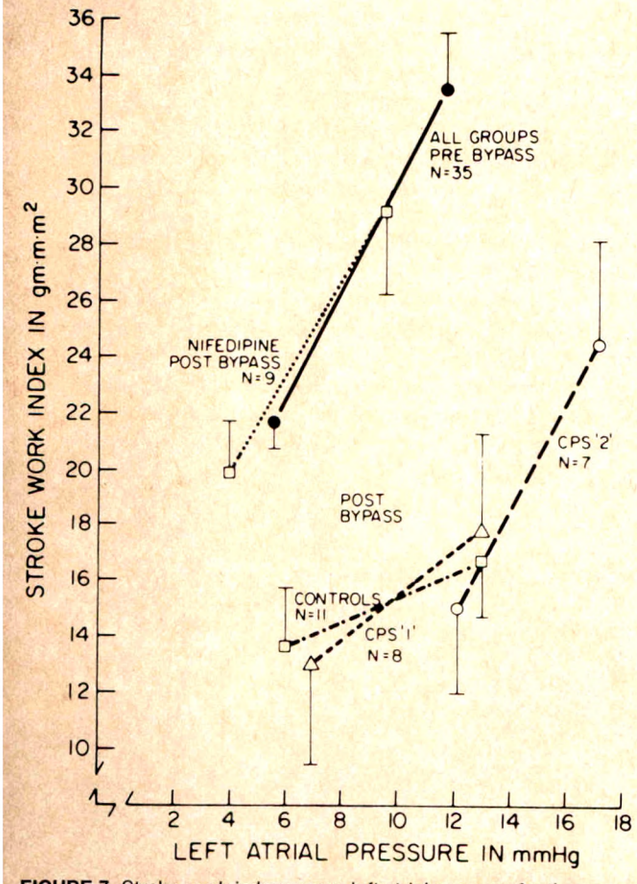

FIGURE 7. Stroke work index versus left atrial pressure for the same 4 groups of dogs as in Figures 1 and 2. Volume loading was achieved with 50 ml incremental infusions of whole blood to a total volume of 500 to 600 ml. Pre- and postischemia function curves are shown. Note that only the group treated with nifedipine-containing solutions achieved a normal work response to increases in preload. CPS = cardioplegic solutions. Reprinted with permission from *Ann Surg.*[39]

These data are summarized in Table VI and Figure 8. Although good protection was achieved with cardioplegic solution, significantly better hemodynamic results were achieved with the nifedipine-treated group. The data from pathology studies demonstrated no differences between the 2 groups.

Hypothermic experiments—3 hours of global ischemia: The experimental protocol was similar to that used for the 1- and 2-hour ischemic experiments. The dogs in this study were divided into 4 groups.

Cardioplegic solution: Ten dogs received seven 500-ml dosages of cardioplegic solutions initiated at the onset of ischemia and every 30 minutes thereafter during the 180 minutes of global ischemia.

Cardioplegic solution plus nifedipine: The 8 dogs in this group received seven 500-ml dosages of cardioplegic solutions containing nifedipine in concentrations of 200 to 300 μg/liter.

Intracellular-like cardioplegic solution: Six dogs received five 500-ml dosages of intracellular-like cardioplegic solution initiated at the onset of ischemia and every 45 minutes thereafter during the 180 minutes of global ischemia.

Intracellular-like cardioplegic solution plus nifedipine: The 6 dogs in this group received 5 dosages of solution containing nifedipine (200 to 400 μg/liter) at 45-minute intervals.

The preischemic and postischemic hemodynamic data are summarized in Tables VII, VIII and IX, and pertinent time-variable, LV function curves and degree of recovery of hemodynamic variables are illustrated in Figures 9 to 12. Before cannulation of the heart, all groups were statistically equivalent in 8 of the 10 variables listed in Table VII. For reasons unknown, the peak dP/dt and mean arterial pressures were increased in the 2 cardioplegic solution groups in comparison to the 2 intracellular-like cardioplegic solution groups before perfusion. Methodology was constant for all dogs in this study.

Two hours after termination of the 3.5- to 4-hour duration of cardiopulmonary bypass, most variables were as expected. In comparison to the prebypass values, there were small changes in dP/dt, peak LV pressure and heart rate, and significant changes in total peripheral resistance, mean arterial, left atrial and LVEDP. These alterations are characteristic of long hypothermic perfusion in dogs.

The 2 base solutions (cardioplegic solution and intracellular-like cardioplegic solution) differed little in resultant cardiac effects, although administered at different time increments (30 versus 45 minutes). The only 2 statistically significant differences were in dP/dt and total peripheral resistance (Table IV). There were no differences in SWI as a function of time (Fig. 9) or in the response to volume loading (Fig. 10).

The addition of nifedipine to cardioplegic solutions had no significant overall effect on postischemic cardiac performance in comparison to cardioplegic solutions

TABLE VI Comparison of 2-Hour Postbypass Values* for Bolus Aortic Root Injections During 2 Hours of Global Ischemia at 18°C

Variable	CPS (n = 8)	Nifedipine CPS (n = 8)	Statistical Comment
Heart rate (beats/min)	154 ± 10	161 ± 9	p = NS
dP/dt (mm Hg·s^{-1})	4,063 ± 458	4,263 ± 298	p = NS
MLAP (mm Hg)	3.3 ± 0.7	3.8 ± 0.9	p = NS
LVP-MAX (mm Hg)	128 ± 13	141 ± 13	p = NS
LVEDP (mm Hg)	4.1 ± 0.7	4.0 ± 0.9	p = NS
MAP (mm Hg)	60 ± 5	71 ± 5	p <0.05
Cardiac output (ml/min)	2,638 ± 245	3,475 ± 238	p <0.05
Stroke volume (ml/beat)	17.1 ± 2	21.6 ± 2.3	p <0.05
Stroke work index (g·m·m^{-2})	14.0 ± 2.5	20.6 ± 2.6	p <0.05
TPR (dynes s cm^{-5})	1,813 ± 268	1,681 ± 169	p = NS

* Mean ± standard error.
MAP = mean arterial pressure. Other abbreviations as in Table V.

alone, although LVEDP and mean left atrial pressure were less than those in the cardioplegic solutions group. The marked depression of diastolic pressure in the cardioplegic solutions, cardioplegic solutions + nifedipine and intracellular-like cardioplegic solution groups resulted in low mean arterial pressure and low LV SWI, although cardiac output and stroke volumes were at preischemic levels.

The addition of nifedipine to the intracellular-like cardioplegic solution resulted in marked changes in one major variable, cardiac output (Fig. 11). Although the postischemic preload in the intracellular-like cardioplegic solution plus nifedipine group was similar to that in the cardioplegic solution plus nifedipine group, the lower heart rate and larger cardiac output yielded a large stroke volume. This, combined with the increased mean arterial pressure, resulted in a normal SWI (Fig. 9) that was approximately 2-fold greater than that observed in the other 3 groups after 3 hours of global ischemia. Additionally, the response to volume loading in the intracellular-like cardioplegic solution plus nifedipine group was in striking contrast to the postischemic performance of the other 3 groups. SWI increased by 65% with a 2-fold increase in left atrial pressure (Fig. 10). Thus, the composition of the cardioplegic solutions strongly influenced the effect of nifedipine.

One possible explanation for the observed differences is that the total sodium load presented to the heart with cardioplegic solutions was too large and the intra- and extracellular compartments became edematous to a degree not seen in the 1- and 2-hour hypothermic experiments. Conversely, it could be argued that a low sodium concentration in a cardioplegic solution augmented the action of nifedipine by maintaining lower extracellular concentrations of sodium ion.

Randomized Clinical Trial of a Calcium-Channel Blocker in Cardioplegic Solution

These studies led to a clinical trial of nifedipine in a cold, hyperkalemic, alkalotic, hyperosmotic cardioplegic

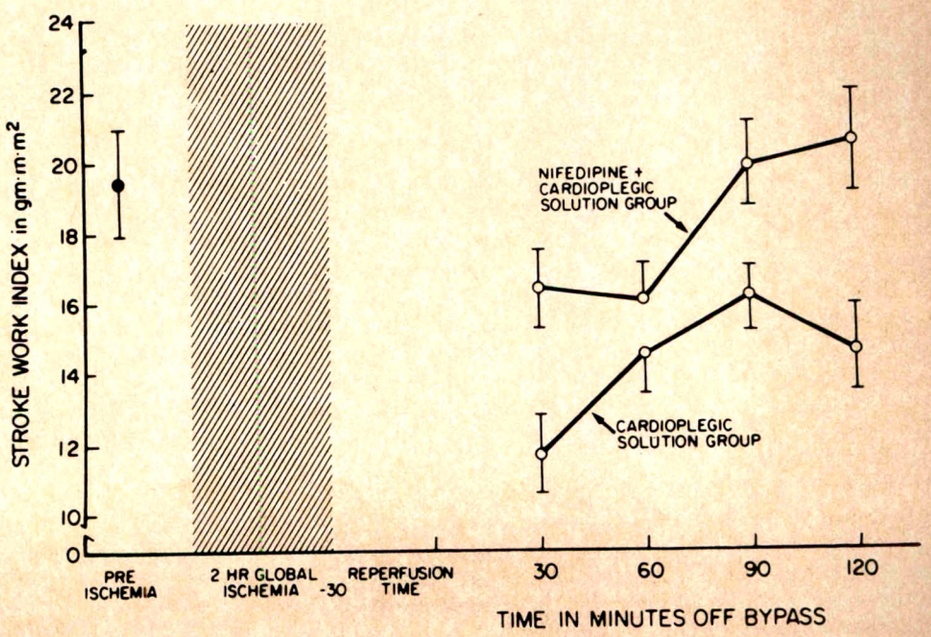

FIGURE 8. Stroke work index versus event and time after bypass for 2 groups of dogs given a clinical cardioplegic solution or the same solution with nifedipine added during 2 hours of global ischemia at an average myocardial temperature of 18°C. Heart rates and left atrial pressures were similar in both groups at the intervals after bypass. Reprinted with permission from *Ann Surg.*[39]

TABLE VII Prebypass and 120-minute Postbypass Values* (3 Hours of Hypothermic Ischemia)

Variable	Preperfusion	Final	% Change	p Value
dP/dt (mm Hg/s^{-1})				
CPS (n = 10)	4,110 ± 277	3,780 ± 272	−8	NS
CPS + N (n = 8)	4,237 ± 292	3,850 ± 392	−9	NS
ICS (n = 6)	3,600 ± 386	2,983 ± 222	−17	<0.025
ICS + N (n = 6)	3,833 ± 439	4,100 ± 321	+7	NS
LVP-Max (mm Hg)				
CPS	160 ± 6	118 ± 9	−26	<0.0005
CPS + N	166 ± 6	127 ± 12	−23	<0.0125
ICS	136 ± 7	112 ± 4	−17	<0.0125
ICS + N	139 ± 5	129 ± 10	−7	NS
LVEDP (mm Hg)				
CPS	2.8 ± 0.6	6.5 ± 1.1	+132	<0.005
CPS + N	3.6 ± 0.5	4.1 ± 0.7	+14	NS
ICS	3.0 ± 0.8	6.6 ± 0.8	+120	<0.0005
ICS + N	3.7 ± 0.8	4.0 ± 0.6	+8	NS
SWI (g·m·m^{-2})				
CPS	22.8 ± 1.7	8.8 ± 1.8	−62	<0.0005
CPS + N	21.5 ± 1.4	9.0 ± 1.8	−58	<0.0005
ICS	18.7 ± 1.8	10.3 ± 1.5	−44	<0.005
ICS + N	20.5 ± 1.7	21.3 ± 2.1	+4	NS
Heart rate (beats/min)				
CPS	161 ± 4	155 ± 6	−4	NS
CPS + N	181 ± 7	171 ± 5	−5	NS
ICS	156 ± 4	145 ± 11	−7	NS
ICS + N	165 ± 5	148 ± 11	−10	<0.025
MLAP (mm Hg)				
CPS	3.2 ± 0.4	7.3 ± 1.0	+130	<0.005
CPS + N	2.6 ± 0.5	4.6 ± 0.4	+73	<0.005
ICS	3.3 ± 0.8	8.0 ± 1.0	+140	<0.005
ICS + N	4.2 ± 0.5	4.8 ± 0.3	+14	<0.05
Cardiac output (liters/min)				
CPS	2.3 ± 0.1	2.2 ± 0.3	−6	NS
CPS + N	2.2 ± 0.1	2.0 ± 0.3	−6	NS
ICS	2.2 ± 0.2	2.0 ± 0.2	−12	NS
ICS + N	2.2 ± 0.1	3.5 ± 0.2	+59	<0.005
TPR (dynes s cm^{-5})				
CPS	4,200 ± 358	1,703 ± 114	−59	<0.0005
CPS + N	4,840 ± 417	2,052 ± 215	−95	<0.0005
ICS	3,847 ± 348	2,705 ± 515	−30	<0.025
ICS + N	4,097 ± 375	1,631 ± 229	−60	<0.0005
SV (ml/beat)				
CPS	14.1 ± 1	14.6 ± 2	+3	NS
CPS + N	12.3 ± 1	12.2 ± 2	−0.5	NS
ICS	14.3 ± 1	13.5 ± 1	−5	NS
ICS + N	13.6 ± 1	24.2 ± 2	+78	<0.005
MAP (mm Hg)				
CPS	120 ± 6	50 ± 4	−58	<0.0005
CPS + N	131 ± 6	55 ± 5	−58	<0.0005
ICS	104 ± 5	67 ± 8	−36	<0.0005
ICS + N	116 ± 6	72 ± 6	−38	<0.0005

* Mean ± standard error of the mean.
CPS = extracellular-type solution; dP/dt = first derivative of left ventricular pressure; ICS = intracellular-like, low sodium, crystalloid solution; LVEDP = left ventricular end-diastolic pressure; LVP-Max = maximum left ventricular pressure; MAP = mean arterial pressure; MLAP = mean left atrial pressure; N = nifedipine added to the solution; NS = not significant; SV = stroke volume; SWI = stroke work index; TPR = total peripheral resistance. Reprinted with permission from *Surgery*.[38]

solution approved by the Food and Drug Administration and the Institutional Review Board of Washington University. The prospective randomized trial was sponsored by the National Heart, Lung, and Blood Institute, and patient enrollment began in May 1980.

Patient selection, classification and special studies: All patients entered into the protocol signed informed consent agreements before the initiation of special studies or use of the drug. Patients thought to be at increased surgical risk were selected for the study by the following criteria: (1) need for replacement of dysfunctioning prosthetic valve(s) with or without additional valve replacement in another position, (2) need for double or triple valve replacement, (3) need for prosthetic valve replacement because of significant coronary artery disease and valvular dysfunction and (4) presence of severe coronary artery disease with poor ventricular function with or without ventricular aneurysm. Patients expected to require these operations were classified by New York Heart Association (NYHA) (classes I to IV), Canadian angina classification (I to IV) and LV functional class.

The last classification was a composite that used (1) increases in LV diastolic volume index (class III, 30 to 50%; class IV, >50%), (2) LV ejection fraction, determined by planimetry of maximal systolic and diastolic phases of right anterior oblique ventriculography and the Dodge-Sandler calculation, equilibrated radionuclide ventriculography, or both, taking the least value, (3) presence of pulmonary hypertension as expressed by the mean pulmonary artery pressure (class III, 30 to 50 mm Hg; class IV, >50 mm Hg) and (4) the cardiac index (class III, 2 to 2.5; class IV, <2 liters min/m^2).

TABLE VIII Statistical Comparison of Final Values*: Dogs Subjected to 3 Hours of Myocardial Ischemia

Variable	CPS (n = 10)	CPS versus CPS + N (p value)	CPS + N (n = 8)	CPS + N versus ICS (p value)	ICS (n = 6)	CPS versus ICS (p value)
dP/dt (mm Hg·s^{-1})	3,780 ± 272	NS	3,850 ± 392	<0.05	2,983 ± 222	<0.025
LVP-Max (mm Hg)	118 ± 9.3	NS	127 ± 12	NS	112 ± 4	NS
LVEDP (mm Hg)	6.5 ± 1.0	<0.05	4.1 ± 0.7	<0.0125	6.7 ± 0.8	NS
SWI (g·m·m^{-2})	8.8 ± 1.8	NS	8.9 ± 1.8	NS	10.2 ± 1.5	NS
Heart rate (beats/min)	155 ± 6	<0.0125	171 ± 5	<0.0125	145 ± 11	NS
MLAP (mm Hg)	7.2 ± 1.0	<0.0125	4.6 ± 0.4	<0.0005	8 ± 1.0	NS
CO (liters/mm)	2.2 ± 0.3	NS	2.0 ± 0.3	NS	2.0 ± 0.2	NS
TPR (dynes s cm^{-5})	1,703 ± 114	<0.05	2,052 ± 215	NS	2,705 ± 515	<0.0125

* Mean ± standard error of the mean.
CO = cardiac output; CPS = extracellular cardioplegic solution; dP/dt = first derivative of left ventricular pressure; ICS = intracellularlike low sodium, crystalloid solution; LVEDP = left ventricular end-diastolic pressure; LVP-Max = maximum left ventricular pressure; MLAP = mean left atrial pressure; N = nifedipine added; NS = not significant; SWI = stroke work index; TPR = total peripheral resistance. Reprinted with permission from *Surgery*.[38]

TABLE IX Statistical Comparison of Final Values*: Dogs Subjected to 3 Hours of Myocardial Ischemia

Variable	ICS + N (n = 6)	Versus CPS (p value)	Versus CPS + N (p value)	Versus ICS (p value)
dP/dt (mm Hg·s^{-1})	4,100 ± 321	NS	NS	<0.005
LVP-Max (mm Hg)	129 ± 10	NS	NS	<0.05
LVEDP (mm Hg)	4.0 ± 0.6	<0.05	NS	<0.0125
SWI (g·m·m^{-2})	21.3 ± 2.1	<0.0005	<0.0005	<0.0005
Heart rate (beats/min)	148 ± 11	NS	<0.025	NS
MLAP (mm Hg)	4.7 ± 0.3	<0.025	NS	<0.0025
CO (liters/mm)	3.5 ± 0.2	<0.0005	<0.0005	<0.0005
TRP (dynes s cm^{-5})	1,631 ± 229	NS	NS	<0.025

* Mean ± standard error of the mean.
Abbreviations as in Table VIII. Reprinted with permission from *Surgery*.[38]

Patients enrolled in the protocol had 5 special serial studies performed throughout various phases of the hospital course. These were radionuclide ventriculography, isoenzyme creatine kinase (CK-MB) assays, Holter electrocardiographic (ECG) recordings, myocardial pyrophosphate scans and operative and postoperative hemodynamics.

Equilibrated radionuclide ventriculography was performed with technetium-99m from which both right and left global ventricular ejection fractions were calculated by computer as well as 8-segment wall motion analysis for each ventricle. These studies were performed 1 to 4 days preoperatively and 24 to 72 hours, 6 to 10 days and 6 to 9 weeks postoperatively.

Twenty-four-hour Holter ECG recordings were made preoperatively, for the first 72 hours postoperatively, and 1 and 6 to 9 weeks after operation using Avionics 2-channel recorders.

Myocardial isoenzyme CK-MB assays were performed by the glass bead method. Samples were obtained the evening before and the morning of operation, before and after the induction of anesthesia, at the time of incision and immediately before bypass. Subsequent samples were obtained at the termination of bypass, then every hour for 3 hours, then every 4 hours for 48 hours, then every 6 hours for 24 hours and finally every 12 hours for 48 hours. In all, 30 samples were taken, covering a minimal continuum of 132 hours. The concentration-time integral value was obtained by computer for the same time frame for all patients starting after perfusion.

Radionuclide myocardial pyrophosphate scans were performed 1 to 3 days preoperatively and 48 to 72 hours, 6 to 9 days and 6 to 9 weeks postoperatively with technetium-99m. Scans were graded from normal to 4+ uptake of isotope in terms of intensity and degree of localization noted.

Intraoperative and postoperative hemodynamic measurements were performed after induction, immediately before and at cessation of bypass, immediately before leaving the operating room, at 1 and 4 hours after arrival in the intensive care unit and every 4 hours

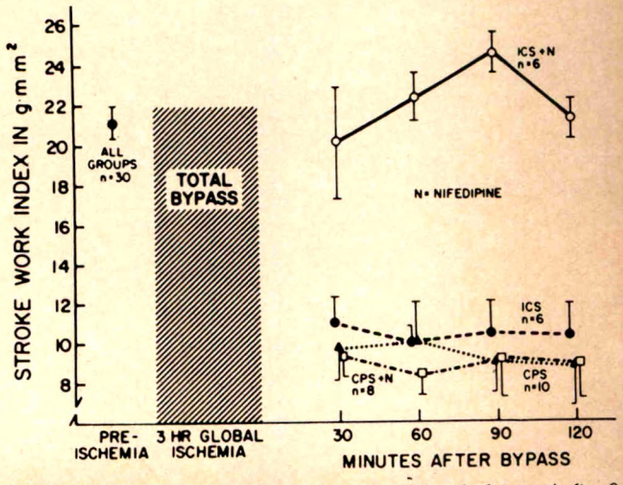

FIGURE 9. Stroke work index as a function of time before and after 3 hours of global myocardial ischemia under hypothermic (10° ± 2°C myocardial) conditions of total cardiopulmonary bypass (25°C) for all 4 groups. CPS = extracellular crystalloid cardioplegic solutions; ICS = intracellular-like, low sodium cardioplegic solutions. Reprinted with permission from *Surgery*.[38]

TABLE X Preoperative Hemodynamics of Randomized Groups*

Measurement†	Treated (n = 39)	Not Treated (n = 35)
LV end-diastolic volume index (70 ± 20 ml/m^2)	103 ± 5.9	106 ± 9.2
Cardiac index (≥2.8 liters/min/m^2)	1.69 ± 0.09	1.73 ± 0.09
LV stroke work index (≥32 g·m·m^{-2})	20 ± 1.7	23 ± 1.9

* Data are shown as mean ± standard error of the mean.
† Normal values given in parentheses.
LV = left ventricular.

TABLE XI Preperfusion Hemodynamics

Variable	Control (n = 27)	Treated (n = 28)
Cardiac output (liters/min)	3,397 ± 182	3,198 ± 167
Cardiac index (liters/min/m^2)	1.8 ± 0.1	1.7 ± 0.1
Stroke volume (ml/beat)	43 ± 4	41 ± 3
Left ventricular stroke work index (g·m·m^{-2})	23 ± 2	20 ± 2
Right ventricular stroke work index (g·m·m^{-2})	3.9 ± 0.4	4.3 ± 0.4
Pulmonary vascular resistance (dynes s cm^{-5})	198 ± 23	166 ± 22
Total peripheral resistance (dynes s cm^{-5})	2,122 ± 161	1,988 ± 158

thereafter for 48 hours. Six to 9 weeks after operation, the principal investigator interviewed each patient, performed a physical examination and reviewed the current list of medications. Statistical analyses were performed using the Student unpaired and paired *t* test and chi-square test with the Yates correction for small numbers.

Randomization: Because nifedipine had never been used before in a cardioplegic solution in man, it was decided that before randomization, 10 patients would be given the drug to ascertain whether or not there were obvious untoward effects at the proposed dosage. Thereafter, assignment to cardioplegia or cardioplegia plus nifedipine was by a flip of a coin.

Operative conditions and cardioplegic administration: Myocardial temperatures were measured before and after infusion of cardioplegic solution and the resultant time-temperature course was integrated. This integral is more representative of the injury-susceptible interval than cross-clamp time alone, because myocardial injury is related to the duration of ischemia at a given temperature. The time-temperature integrals for the 2 groups were statistically similar for the cardioplegia and nifedipine groups, respectively (1,124 ± 129 versus 1,283 ± 83°C·minutes). The method of cardiopulmonary bypass was similar in all patients operated upon within the study period. A bubble oxygenator, roller pump, arterial line filter and hemodilution were used. The priming volume and composition were standardized, as were the anesthetic techniques.

The method used for administration of cardioplegic solution was identical for all the protocol patients. Each plastic bag containing the cardioplegic solution was evacuated of all air and covered with a brown plastic bag

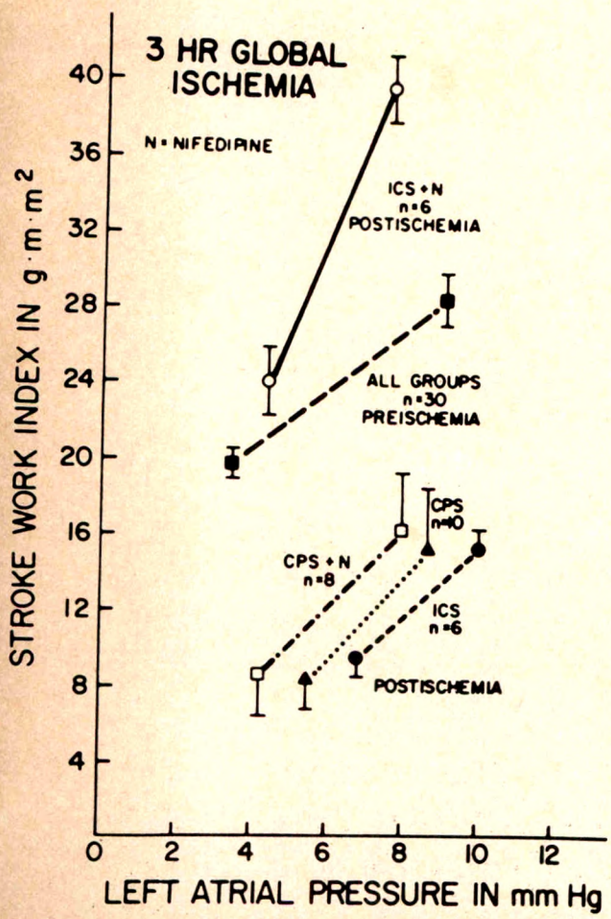

FIGURE 10. Stroke work index versus left atrial pressure before and after volume-loading tests with 500 ml of blood, before and 100 minutes after 3 hours of global ischemia under hypothermia (10° ± 2°C) and hypothermic (25°C) total cardiopulmonary bypass for all 4 groups. CPS = extracellular crystalloid cardioplegic solutions; ICS = intracellular-like, low sodium cardioplegic solutions. Reprinted with permission from *Surgery*.[38]

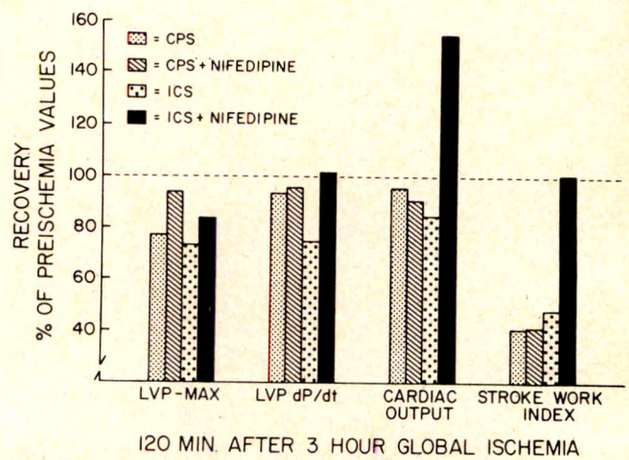

FIGURE 11. Percent recovery of indexes of left ventricular function. Comparison of 120-minute postischemia values for all 4 groups subjected to 3 hours of hypothermic (10° ± 2°C) global myocardial ischemia. CPS = extracellular crystalloid cardioplegic solutions; ICS = intracellular-like, low sodium cardioplegic solutions; LVP dP/dt = first derivative of left ventricular pressure; LVP-Max = maximum left ventricular pressure. Reprinted with permission from *Surgery*.[38]

TABLE XII Postperfusion Hemodynamics

Variable	Control (n = 27)	Treated (n = 28)	Percent Change* Control (n = 27)	Percent Change* Treated (n = 28)
Cardiac output (liters/min)	4,101 ± 215	4,536 ± 116	+21	+42
Cardiac index (liters/min/m^2)	2.3 ± 0.2	2.5 ± 0.1	+28	+47
Stroke volume (ml/beat)	50 ± 3	56 ± 3	+16	+37
Left ventricular stroke work index (g·m·m^{-2})	27 ± 2	28 ± 2	+17	+40
Right ventricular stroke work index (g·m·m^{-2})	5.9 ± 0.9	6.2 ± 0.5	+51	+44
Pulmonary vascular resistance (dynes s cm^{-5})	250 ± 36	146 ± 16	+26	−12
Total peripheral resistance (dynes s cm^{-5})	1,727 ± 178	1,362 ± 87	−19	−31

* Percent change between data obtained before perfusion and those obtained after perfusion.

because of the sensitivity of nifedipine to light. Ingredients were added and the bags were maintained in the operating room on a bed of ice in a polystyrene container.

Each bag was connected to a 3/16 in (inner diameter) clear polyvinyl chloride tubing, which was connected to a DLP cannula (12 or 14 gauge) in the aortic root or to DeBakey coronary artery perfusion cannulas if the aorta was open. The bag was inserted into a pressurized infusion bag with the bladder pressure regulated at 80 to 150 mm Hg. Infusions were timed and the pressure was regulated to control the solution flow at 200 to 300 ml/min, which approximates normal human coronary artery flow of 80 ml/100 g heart weight/min. Flow calculations were performed by use of a spring scale calibrated in milliliters, which was accurate by our testing to ±4%. The solutions (500 to 1,000 ml) were infused every 30 ± 3 minutes.

The total amounts of drug and ion load to each heart were dependent on the ischemic interval. Potassium and lidocaine concentrations were decremental, as were sodium bicarbonate and tromethamine additions, because less of the latter 2 drugs was required to maintain an average pH of 7.8 at 37°C when the volumes of acidic solutions of the former 2 additives were decreased. The concentrations of potassium used per bag of cardioplegic solution were as follows: potassium chloride 25, 15, 10, 5 and 5 mEq/liter. Lidocaine concentrations were decreased in the cascade of 200, 100, 50, 25 and 0 mg/liter. Each bag was sampled for pH, carbon dioxide partial pressure, oxygen partial pressure, calculated bicarbonate radical and base excess by an ABL2 Radiometer analyzer (Radiometer A/S). Periodically, samples were sent to the Clinical Chemistry Laboratory for ionic, osmolar and drug analyses as a quality control measure. Nifedipine was added in a darkened room in constant amounts to each bag after other ingredients were added, to yield an average final concentration of 275 μg/liter.

Results: The preoperative assessment of the 39 treated and 35 nontreated patients was similar. The NYHA functional classes were 3.5 and 3.7 ± 0.1, angina class 1.5 and 1.8 ± 0.3 and LV functional class 3.2 and 3.4 ± 0.2, respectively. Distributions by age, sex, previous myocardial infarction, presence of atrial fibrillation and cardiomegaly, ejection fractions, ventricular ectopy rates, type of operation and surgeon were nearly identical. Comparative hemodynamic assessment before operation is shown in Table X. Further hemodynamic data obtained after induction of anesthesia but before opening of the chest are shown in Table XI and are similar. These data are for patients not requiring inotropic drugs or an intraaortic balloon pump; hence the number in each group is less than the total in the treated and nontreated groups.

The incidence of acute low cardiac output was 23% (8 of 35) in the nontreated group and 15% (6 of 39) in those receiving nifedipine in the cardioplegic solution (p = NS). One half of each group survived the interval of extreme low flow state, yielding short-term (1 to 72 hours postoperative) mortality rates of 11.5 and 7.5%, respectively (p = NS).

The primary effect of the addition of nifedipine was a short-lived hemodynamic one (Table XII). The percent change in cardiac index, stroke volume and LV stroke work in the treated group was nearly twice that observed in the group receiving cardioplegic solution only. Additionally, there were marked differences in the pulmonary and systemic vascular resistances.

A difference of nearly 40% between the 2 groups was present with respect to pulmonary vascular resistance. Patients treated with cardioplegic solution lacking nifedipine had an increase in this variable (26%), whereas those given cardioplegic solution with nifedipine had a small decrease of 12%. The decrease in total peripheral resistance was also greater in the nifedipine-treated group. There were no statistically significant differences

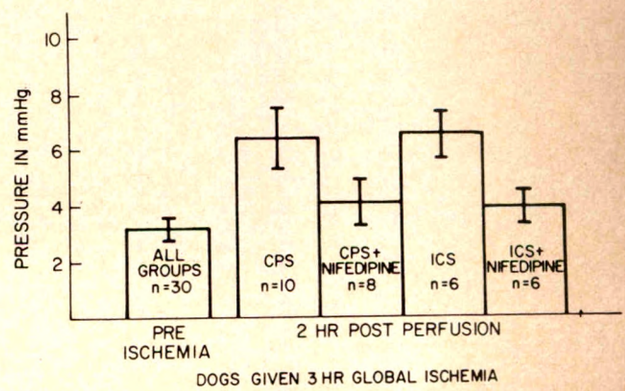

FIGURE 12. Preservation of left ventricular end-diastolic pressure in all groups subjected to 3 hours of hypothermic (10° ± 2°C) global myocardial ischemia under spaced multiple doses of 4 different myocardial protective solutions. Comparison of 120-minute postischemia values for each group to the preischemic values of all groups jointly. CPS = extracellular crystalloid cardioplegic solutions; ICS = intracellular-like, low sodium cardioplegic solutions. Reprinted with permission from *Surgery*.[38]

for heart rate, mean arterial pressure or right ventricular SWI between the 2 groups in the interval after perfusion.

Other studies: The technetium-99m pyrophosphate scans obtained were technically adequate in 34 patients treated with cardioplegic solution containing nifedipine and in 29 who had cardioplegic solution alone. In no patient receiving nifedipine did the blinded grading of the myocardial injury scan increase. Thirty of the 34 had no change and 4 had improvement. Of the 29 patients receiving cardioplegic solution alone, 20 had no change and 5 had improvement. However, 4 had a pattern of discrete injury postoperatively, which was not present on the preoperative examination. The CK-MB determinations, radionuclide ventriculograms and Holter recordings did not show any differences between the treated and control randomized groups.

Discussion

The concordant data obtained in the animal experiments reported here demonstrated a high degree of efficiency of the calcium-channel blocking agent nifedipine. The effects were dramatic and consistent, especially when the time interval of ischemia was prolonged either at normothermia or at low myocardial temperatures. The results of the randomized clinical trial were not as dramatic as those of the animal studies. The major findings were the difference in the hemodynamic status of the treated patients immediately after the cessation of cardiopulmonary bypass, and the difference in injury patterns as seen by myocardial scans. The benefit or lack thereof of continuation of nifedipine in the postoperative phase is unknown. No patient entered into this study was receiving a calcium-channel blocker before surgery and none received such an agent immediately after surgery.

The specific hypothesis of these studies was that nifedipine would decrease the incidence of acute low output syndrome and death. Although a trend toward this goal was shown, the use of the drug clearly did not eliminate this cause of death.

The hemodynamic assessments and myocardial scan data show that preservation was improved with nifedipine. Use of a calcium-blocking agent will not enhance biochemical energy stores; it will only retard the rate of degradation as shown by adenosine triphosphate studies during coronary artery bypass operation. Patients who are critically ill and have little reserve, therefore, remain at risk for myocardial power failure after global ischemia and reperfusion. Thus, use of nifedipine in cardioplegic solutions must be viewed as an adjunct and not a panacea for the prevention of myocardial injury in clinical surgery.

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Calcium-Channel Blockers in the Treatment of Migraine

H. J. GELMERS, MD, PhD

According to classic theory, a migraine attack is initiated by cerebrovascular spasm followed by extracranial vasodilatation. Results of recent studies support this theory and suggest that cerebral blood flow during the initial phase of migraine symptoms is, in fact, decreased and this decrease probably leads to ischemia and hypoxia. Cellular hypoxia, in turn, can cause an increase in the flow of calcium from the extracellular fluid to the intracellular space, resulting in calcium overload and cellular dysfunction. Because calcium-channel blockers selectively inhibit the intracellular influx of calcium ions, investigators have begun evaluating the efficacy of these agents for migraine prophylaxis. Nimodipine, a calcium-channel blocker that exhibits selective effects on cerebral vessels, seems to offer protection against the cerebral ischemia and hypoxia presumed to be operative during migraine attacks. In a double-blind, placebo-controlled study, nimodipine decreased the frequency and duration of migraine attacks by at least half in 69% of patients treated with this agent. Comparable reductions in migraine frequency and duration were attained in 58, 51, 41 and 52% of patients treated with methysergide maleate, pizotifen, clonidine hydrochloride and propranolol, respectively. The piperazine derivative flunarizine also has calcium-channel blocking properties. This agent prevents vasospasm in cerebral arteries and protects against cerebral hypoxia. Results of double-blind studies of migraine prophylaxis with flunarizine demonstrate the beneficial effects of this agent, particularly in younger patients. Flunarizine proved to be superior to pizotifen in decreasing the severity of migraine attacks and comparable to pizotifen in decreasing their frequency. Thus, it appears that the prophylactic effects of calcium-channel blockers such as nimodipine and flunarizine are comparable to, if not better than, those achieved with some of the more frequently prescribed migraine preventives.

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Several theories have been proposed to explain the mechanisms responsible for migraine attacks. Treatment selection often varies, depending on which theory a physician considers most plausible. Recently, investigators have suggested that diminished cerebral blood flow leading to hypoxia and intracellular calcium overload may be responsible for triggering migraine symptoms. Based on this hypothesis, calcium-channel blockers, which inhibit the intracellular flux of calcium, may offer a new prophylactic alternative for migraine sufferers.

Beginning with a basic description of migraine classification and pathophysiologic features, this report reviews the different theories of migraine origin. Major attention is focused on the potential role of hypoxia in migraine pathophysiologic features and the investigative findings that support the use of calcium-channel blockers for prevention of migraine attacks.

From the Department of Neurology, Pr. Irene Ziekenhuis, NL-7607 Almelo, CBF-laboratory, Department of Neurosurgery, Academic Hospital, NL-9700, Groningen, The Netherlands.

Address for reprints: H. J. Gelmers, MD, Department of Neurology, Pr. Irene Ziekenhuis, NL 7607 Almelo, The Netherlands.

Types of Migraine

In clinical practice, the diagnosis of migraine is based on recurrent, severe, throbbing headaches, frequently unilateral in onset and usually associated with anorexia, nausea and vomiting. Some patients may have prodromal or concurrent neurologic symptoms and mood disturbances.[1] The nature and severity of associated symptoms determine whether the migraine is classified as *classic*, *common*, or *complicated*.[2]

Classic migraine begins with an aura of neurologic symptoms that are usually, but not always, visual. The most characteristic feature of the visual aura is the "fortification spectrum," which usually persists for about 20 minutes. The spectrum beings as a central or paracentral scotoma that enlarges in a semicircular pattern, forming a scintillating and serrated shape suggestive of a fort's embattlements. The flickering pattern becomes increasingly larger and more irregular as it approaches the periphery of the visual field and

then disappears. Visual symptoms are typically followed by a unilateral, throbbing headache that lasts for several hours and is accompanied by anorexia, nausea and vomiting. The patient usually recovers after a night's sleep.

Common migraine, which is what most migraine sufferers have, includes the throbbing headache and attendant gastrointestinal symptoms without the neurologic aura.

Complicated migraine is distinguished by neurologic features that are so severe they often obscure the diagnosis of migraine and may result in a persistent neurologic deficit.

Migraine Pathophysiologic Features

The classic theory of migraine development attributes the neurologic aura to intracerebral vasoconstriction, which induces the extracranial vasodilatation responsible for the severe headache. During the 1930s and 1940s, Wolff[3] wrote a series of reports supporting and developing this theory. One of his more noteworthy findings was the disappearance of the visual aura in patients who inhaled amyl nitrite, a well-known vasodilator. This discovery was considered incontrovertible evidence that the aura was caused by vasoconstriction. Their additional findings favoring vasodilatation as the cause of the headache included the throbbing, pulsatile nature of the headache; the associated dilatation and tenderness of the superficial temporal artery; and the disappearance of symptoms after compression of the internal carotid artery or treatment with the vasoconstrictor ergotamine.

Differing theories have evolved to explained the events that characterize a migraine attack. Two of the more widely recognized are described as follows.

Humoral model: Wolff suggested the possibility that humoral control of cranial vessels is defective during a migraine attack. He and his associates[4] isolated what they called "headache stuff," which was subsequently identified as substances that accumulate around dilated cerebral arteries and sensitize them to pain. A number of such substances have been identified as possible contributors to migraine symptoms. These include amines (serotonin, catecholamines, histamine and tyramine), polypeptides (bradykinin and angiotensin), prostaglandins and adenosine monophosphate.

The humoral theory of migraine origin is supported by a cyclic sequence of events detected in patients who have *classic* migraine attacks. The cycle begins with an increase in the plasma norepinephrine concentration during the prodromal, or neurologic, phase.[5] The increased norepinephrine concentration serves to exacerbate the already increased platelet aggregation present in many migraine patients.[6] The release of serotonin and adenosine diphosphate from the aggregated platelets perpetuates the cycle by causing an even greater increase in platelet aggregation.

Serotonin is capable of exerting complex vascular effects that can lead to arterial constriction and capillary dilatation[7]; serotonin depletion elicits an opposite set of reactions.[8] Serotonin also increases the permeability of the blood-brain barrier and thereby promotes its own entry into the brain.[9] In migraine patients, serotonin seems to facilitate the intracranial arterial vasoconstriction leading to neurologic symptoms, which are usually visual. In time, the serotonin concentration decreases, and the tonic constricting effect subsides.

The decrease in serotonin concentration may contribute to the extracranial vasodilatation and associated headache, but it is probably not the sole cause of the headache. The release of neurokinins from aggregated platelets and mast cells is thought to sensitize pain receptors in the walls of extracranial vessels,[10] which would explain the tenderness in the scalp and neck vessels often associated with an acute migraine attack.

Although the sequence of aforementioned events described seems to be well accepted, more recently acquired data seriously challenge this explanation of migraine pathophysiologic make-up and suggest that the "hypoxia model" described as follows may be a more likely scenario.

Hypoxia model: Results of blood flow studies conducted during the late 1960s and early 1970s[11,12] supported the classic theory of vasoconstriction followed by vasodilatation; cerebral blood flow was reported to decrease during the aura, or neurologic phase, and to increase during the headache phase. However, within the past few years, preliminary findings obtained with more direct methods for measuring cerebral blood flow indicate that a different sequence of events may occur.

Olesen et al[13] reported the rather startling finding that oligemia, rather than hyperemia, characterized the headache phase of classic migraine. Even in several patients who had focal hyperemia as the initial migraine event, there was no evidence of hyperperfusion during the headache phase. The oligemia began in the occipitoparietal region and spread forward, gradually encompassing the entire hemisphere. Because the spread of oligemia was not in accordance with the territories supplied by the larger cerebral arteries, the investigators thought it was unlikely that the migraine was caused by spasm of these vessels. These findings led to the suggestion that the vascular changes associated with migraine attack may be secondary to a primary event in the cerebral parenchyma.

Cerebral blood flow studies in patients with *common* migraine have yielded conflicting results. Although some investigators found no alterations in blood flow, either focal or global,[14] others reported changes similar to those observed by Olesen et al in patients who suffer from *classic* migraine.[15]

The spread of the migrainous visual aura (the fortification spectrum) during the neurologic phase resembles the progression of Leao's "spreading cortical depression," an inhibitory wave that is preceded by a phase of short-lived neuronal activation.[16] This resemblance has led to the suggestion that the migrainous visual aura and the spreading cortical depression may be one and the same. Animal experiments have shown that spreading cortical depression can be chemically triggered. For example, the application of potassium chloride to the cerebral cortex has been shown to elicit

this depression.[17] It is therefore conceivable that localized cerebral hypoxia initiates the spreading cortical depression typical of migraine attacks by inducing focal increases in cerebral extracellular potassium levels.

As mentioned in the discussion of the humoral model, norepinephrine and therefore the sympathetic nervous system, may contribute to the genesis of a migraine attack. Migraine sufferers seem to have a persistent degree of vasoconstriction during headache-free intervals. This finding has been interpreted as a sign of excessive sympathetic tone. An adrenergic system has been demonstrated to be diffusely present in the pontine and medullary regions of the brain, and also in a well-localized area, the locus ceruleus.[18] From these areas, the system projects anteriorly, terminating both synaptically and as free boutons. There is evidence indicating that the effects of the central sympathetic system on cerebral blood flow and vascular permeability are similar to the effects of the peripheral sympathetic system on the peripheral vasculature.[19] Hence, it is possible that the peripheral humoral changes noted during a migraine attack merely reflect critical alterations in neurohumoral activity.

In the context of migraine-associated hemodynamic changes, it is important to mention that a migraine attack is often preceded by a state of arousal. Arousal can cause focal increases in cerebral metabolism, increasing local tissue requirements for oxygen. As the need for oxygen increases, vessels in the surrounding area dilate to ensure that blood flow is sufficient to satisfy this need. (It should also be noted that a general state of arousal is usually associated with an increase in catecholamine secretion, which can lead to the changes described previously.)

It is tempting to speculate that any increase in sympathetic tone involving cerebral circulation decreases the vasodilatory response to local tissue acidosis as well as to hypercapnia or hypoxia.[20] Therefore, it is possible that excessive sympathetic tone prevents cerebral vessels from dilating sufficiently to match the increased requirement for oxygen. Such an uncoupling between supply and demand can lead to cerebral hypoxia, the event believed to trigger a migraine attack.

The cerebral hypoxia model of migraine origin derives primarily from studies of regional cerebral blood flow. The remarkable similarities between cerebral hypoxia and "spreading cortical depression" lead one to assume that focal brain hypoxia occurs early in the migraine attack, giving rise to the "spreading cortical depression." According to this model, the cortical depression would be the result rather than the cause of brain hypoxia. The neuronal activation that precedes the depression wave would temporarily increase oxygen demand and, thus, aggravate the early hypoxia.

There is more direct evidence that hypoxia occurs during a migraine attack. Such evidence includes biochemical alterations typical of brain hypoxia[21,22] and, in severe cases of migraine, organic brain changes, ranges from cerebral edema to permanent ischemic lesions.[8,23]

The hypoxia model suggests that cerebral hypoxia occurs in every attack of migraine, but whether the hypoxia, along with the associated spreading wave of cortical depression, manifests as neurovisual phenomena depends on the severity of the hypoxia and its location in the brain. Whether an episode of hypoxia will lead to a full-blown migraine attack depends largely on the nature of the ensuing whirlpool of biochemical and vascular changes.

Treatment

Migraine patients' conditions can be managed either by treating symptoms once an attack is underway (symptomatic therapy) or by preventing the attack altogether (prophylactic therapy). However, symptomatic treatment is usually not as effective as preventive therapy. Pharmacologic agents that will terminate an attack include various ergotamine derivatives combined with caffeine (which acts synergistically with the ergot alkaloids), antispasmodics, sedatives and antiemetics.

The various models of migraine origin can provide clues for developing additional therapeutic approaches for interrupting or preventing the pathophysiologic sequence of events that leads to a migraine attack. The humoral model, although based on concepts that remain to be conclusively substantiated, suggests a wide range of symptomatic and prophylactic treatment options. Because the placebo response in migraine trials ranges from 20 to 40%, a response rate of at least 50% is considered necessary to substantiate therapeutic effect.[24] Regimens based on the humoral model have been described in detail by Friedman,[25] and will not be reviewed here. The remainder of this discussion focuses on treatments founded on the hypoxia model of migraine origin.

If, as many investigators suspect, a hypoxic focus is essential to the onset of a migraine attack, it is logical to assume that the attack will not occur if hypoxia can be prevented. Therefore, drugs that protect the brain from hypoxia may be useful in preventing migraine attacks. Calcium-channel blockers are an obvious choice. In several tissues, cellular hypoxia induces excessive calcium influx across the cell membrane, leading to cellular dysfunction. Using calcium-channel blocker therapy to inhibit this massive shift in calcium concentration appears to prevent cellular dysfunction and improve cerebral tissue perfusion.

Nimodipine treatment: Nimodipine, a dihydropyridine derivative, is a new calcium-channel blocker that has been shown to dilate cerebral vessels[26] and to protect against cerebral ischemia and hypoxia.[27] It is the most potent, and possibly the most selective, cerebral vasodilator of the calcium-channel blockers currently being studied. Its therapeutic profile, therefore, seems ideally suited to migraine prophylaxis.

To date, 2 clinical studies have examined the efficacy of nimodipine in the prevention of migraine symptoms. In a double-blind, placebo-controlled evaluation of prophylactic treatment with this agent, it was found that nimodipine significantly decreased the frequency of migraine attacks.[28] In a similar study, 69% of patients treated with nimodipine had ≥50% decrease in the

TABLE I Response to Migraine Prophylaxis*

Agent	Patients With ≥50% Improvement (%)
Methysergide maleate	58.3
Pizotifen	50.9
Clonidine hydrochloride	40.9
Propranolol	51.6
Amitriptyline	72.0
Nimodipine	69.0

* Adapted from Cough JR, Hassanein RS. Amitriptyline in migraine prophylaxis. Arch Neurol 1979;36:695–699.

frequency and duration of migraine attacks (Fig. 1); however, the severity of the headache once it occurred was reduced to a lesser extent.[29] The level of response to nimodipine was comparable to or better than that obtained with other migraine prophylactic agents (Table I).

Adverse effects noted in associated with nimodipine therapy were minimal. During the initial days of treatment, a few patients reported mild abdominal discomfort, which was attributed to obstipation resulting from relaxation of intestinal smooth muscle. No episodes of hypotension or reflex tachycardia were observed.

Flunarizine treatment: Flunarizine, a difluorated piperazine derivative, is another calcium-channel blocker that has been used in clinical investigations of migraine prophylaxis. This compound has been shown to prevent vasospasm in cerebral arteries;[30] consequently, it was suggested that flunarizine might be effective in preventing ischemia and in protecting against ischemia-induced cellular dysfunction by preventing intracellular calcium overload.[31,32]

Three double-blind investigations have evaluated the efficacy of flunarizine in migraine prophylaxis. Study populations were limited to patients with a diagnosis of *classic* or *common* migraine. One study showed that flunarizine decreased the frequency but not the severity of migraine attacks in younger patients.[33] Another showed that the effects of flunarizine were largely comparable to those of pizotifen.[34] (Pizotifen, a serotonin antagonist, was the first agent considered safe for prevention of migraine and remains the standard against which all migraine prophylactic agents are compared.) Although the 2 agents produced similar decreases in the frequency of attacks, flunarizine proved to be superior in decreasing the severity of the attacks. The third study compared the effects of flunarizine with those of cinnirazine, a piperazine derivative with some calcium antagonistic properties. Results of this study indicated that the drugs were comparable in their ability to decrease the frequency and duration of migraine attacks.[35]

Daytime sedation was the most frequent adverse effect noted in association with flunarizine therapy. However, the sedative effect was not considered sufficiently severe to impede long-term treatment.

In summary, currently available clinical and research findings are compatible with the hypothesis that cerebral hypoxia induced by hypoperfusion is causally related to migraine onset. Identification of this pathophysiologic mechanism, together with the recognition that the hypoperfusion might be related to vasospasm, led to the investigative use of calcium-channel blockers for preventive therapy in patients with migraine. Results of clinical studies suggest that the prophylactic effects of these agents are comparable to, if not better than, those achieved with more standard migraine preventive agents.

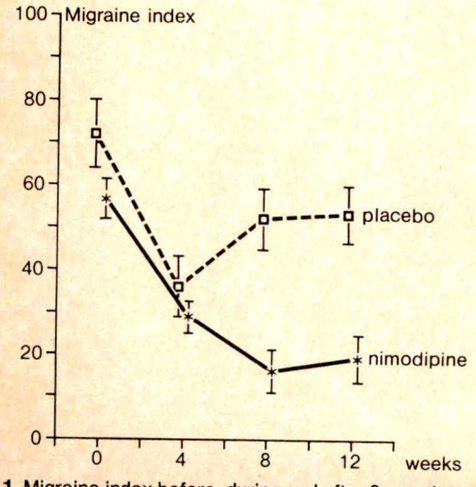

FIGURE 1. Migraine index before, during and after 3-month treatment with nimodipine, 120 mg daily (n = 28), or placebo (n = 22). Migraine index is composite representation of number, severity and duration of migraine attacks. At end of 3 months, migraine index for nimodipine-treated patients was significantly better ($p < 0.01$) than that for control subjects.[29]

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Calcium-Channel Blockers: Effects on Cerebral Blood Flow and Potential Uses for Acute Stroke

H. J. GELMERS, MD, PhD

Current research suggests that ischemia induces a massive shift of calcium from the extracellular fluid to the intracellular space. This is associated with a precipitous decrease in the concentration of adenosine triphosphate, the energy source required to drive the ion pumps of the calcium channels that maintain intracellular calcium homeostasis. The result is a further increase in free intracellular calcium, leading to calcium overload and thus to cell catabolism and cell necrosis. Treatment with calcium-channel blockers may therefore offer a new approach to arresting and, possibly, preventing destruction of cerebral tissue in stroke victims. Animal studies using nimodipine, a calcium antagonist with marked vasodilator effects, have shown that this agent prevents both spasm of the isolated rabbit basilar artery, produced either by depolarization or by receptor stimulation, and postischemic impairment of cerebral blood flow (CBF), which may be a major contributor to neuronal damage. In patients with acute ischemic stroke, intravenous nimodipine therapy caused a dose-dependent increase in hemispheric CBF. These data prompted us to conduct a prospective, single-blind, randomized trial of 60 patients to determine whether nimodipine treatment would reduce neurologic deficits in patients with acute ischemic stroke. The 29 treated patients were given standard dextran therapy supplemented with daily 120 mg doses of nimodipine, and the 31 control subjects received dextran therapy alone. Mathew scale neurologic scores indicated decreased consciousness and impaired cerebral function in both treated and control groups; however, cerebral deficits were significantly smaller in patients who received nimodipine. Adverse effects were minimal and clinically insignificant. These preliminary results suggest that calcium shifts can greatly influence the extent of cerebral damage in stroke victims and calcium antagonists may be useful in treating such patients.

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Despite major advancements in our understanding of the pathophysiologic features of the cerebral circulation, very little progress has been made in our ability to arrest or prevent the functional impairment that often follows acute ischemic stroke. As we continue to learn about the mechanisms that control cerebral blood flow (CBF), we realize that the extent of irreversible cerebral damage is governed by both the duration of ischemia and the rate of blood flow within the ischemic area. In addition, there is evidence suggesting that ischemia-induced shifts of calcium from extracellular to intracellular sites also influence the degree of cerebral functional impairment.

As a result of these findings, physicians are beginning to consider new pharmacologic approaches to managing stroke victims. Most recently, investigations have focused on the potential of calcium-channel blockers to minimize neurologic deficits by altering CBF in ischemic regions. The discussion that follows describes research that culminated in the investigative use of the calcium antagonist nimodipine to treat stroke victims.

From the Department of Neurology, Pr. Irene Ziekenhuis, NL-7607 Almelo; CBF-laboratory, Department of Neurosurgery, Academic Hospital, NL-9700, Groningen, The Netherlands.

Address for reprints: H. J. Gelmers, MD, Pr. Irene Ziekenhuis, NL-7607 Almelo, The Netherlands.

Cerebral Blood Flow and Neurologic Function

Animal studies examining the relation between CBF and neurologic function have led to the definition of flow thresholds that correlate with the severity of cerebral dysfunction. Results of these studies indicate that when the perfusion rate decreases below a certain threshold (about 20 ml/min/100 g), cerebral function becomes impaired.[1–4] A further sustained decrease in CBF to below the critical limit of 8 to 10 ml/min/100 g can lead to irreversible functional impairment. The upper level is known as the "flow threshold for failure of neuronal function,"[5] and the lower level is referred

to as the "flow threshold of membrane failure."[6] When the perfusion rate within an ischemic area ranges between these 2 thresholds, the condition is known as "ischemic penumbra."[5]

Principles of Cerebral Blood Flow Measurements

The development of reliable techniques for measuring CBF has contributed substantially to our knowledge of the mechanisms governing normal CBF and those responsible for the flow derangements that occur in patients with acute ischemic stroke. All current methods for assessing CBF can be traced to Kety and Schmidt,[7] who, in 1945, described the use of an indicator injection technique, based on the Fick principle.

In 1961, Lassen and Ingvar[8] reported a significant advance in CBF monitoring. Their procedure is founded on the assumption that the perfusion rate within a particular tissue can be determined from the rate at which a freely diffusible and inert indicator is cleared by that tissue. If, for example, a gamma-emitting isotope is used as the indicator, the clearance rate of this isotope can be recorded noninvasively by scintillation detectors placed on the patient's head. From the clearance rate, the physician can obtain a clearance curve, and, from the clearance curve, the CBF can be calculated using 1 of several methods. Recording the isotope clearance from many fairly small areas of the brain by means of multiple scintillation detectors allows determination of regional cerebral blood flow (rCBF). The principles and techniques of rCBF calculation have been described in depth by several investigators[9–11] and will not be reviewed here.

Because neurologically healthy persons rarely undergo CBF evaluations, true normal rCBF values are not readily obtainable. Nevertheless, most study populations include at least a few patients who are without evidence of organic brain disease. Normal rCBF values derived from such patients typically vary from 45 to 60 ml/min/100 g, depending upon the measuring technique and method of CBF calculation used.[9] Normal rCBF is nonhomogeneous under resting conditions. A normal rCBF pattern obtained at rest in a silent room with the patient's eyes closed is characterized by high flow rates in the precentral, premotor and frontal regions and by low flow rates in the temporal regions.[12]

The physiologic mechanisms that control rCBF are complex, but, for the purposes of this discussion, can be described as a series of interdependent factors. CBF is ultimately regulated by the metabolic activity of neuronal tissue. An increase in neuronal metabolism augments carbon dioxide (CO_2) production. The increase in CO_2 concentration decreases extracellular pH and causes cerebral vasodilation leading to increased CBF. When neuronal activity diminishes, an opposite scenario occurs: CO_2 production diminishes causing a decrease in cerebral vasodilation and CBF.

Hemodynamic Disorders

In most patients with acute ischemic stroke, the involved hemisphere shows decreased perfusion, which is sometimes attended by a transient decrease in blood flow in the contralateral hemisphere. This remote effect has been attributed to a transneuronally mediated depression of metabolism.[13,14]

Within the ischemic hemisphere, the perfusion rate can vary from region to region. Focal areas of decreased CBF tend to occur within the infarcted area whereas hyperemic regions can sometimes be found at the periphery of the infarct.[15] The presence of hyperemic areas is described as the "luxury perfusion syndrome" and has been attributed to local metabolic acidosis.[16]

Derangements in CBF autoregulation have been observed in stroke patients. Autoregulation of CBF is defined as the inherent ability of the cerebral vasculature to maintain a constant blood flow over a wide area of cerebral perfusion pressure. The upper and lower limits of the mean arterial blood pressure required to maintain CBF within a normal range are 50 and 160 mm Hg, respectively.[17,18] After stroke, autoregulation is often lost, presumably because the vessels supplying the ischemic region are maximally dilated. As a result, CBF becomes pressure-dependent at all levels of perfusion pressure. (Some patients with global loss of autoregulation have a focal parodoxical response to an increase in blood pressure.[19] The increase in blood pressure is thought to increase intracranial pressure, causing increased cerebrovascular resistance in the infarcted area and, consequently, a decrease in rCBF. Normal autoregulatory function may return within days or weeks of the ischemic episode.) In addition, the normal response of cerebral tissue to CO_2 may be decreased or absent, and paradoxical reactions may occur. These paradoxical reactions, characterized by a decrease in CBF in response to CO_2, have been attributed to the following processes. Ischemic areas probably lose their responsiveness to CO_2 as a result of accumulated acid metabolites, mainly lactic acid, whereas the more normal surrounding areas remain reactive to CO_2. In the presence of hypercarbia, the vessels in the periischemic area dilate, creating a zone of decreased cerebrovascular resistance and decreased perfusion pressure surrounding the ischemic region. The decrease in perfusion pressure diminishes the blood flow within the ischemic area. This set of conditions is often described as the "intracerebral steal syndrome."[20]

Role of Calcium in Ischemic Cell Damage

Recently, the importance of calcium in ischemic cell damage has been the focus of considerable discussion and investigation. Schanne et al[21] were among the first to support the hypothesis that calcium plays a major role in the pathophysiologic features of cell injury. They showed that a wide range of membrane-active toxins can cause toxic cell death only in the presence of a normal extracellular calcium concentration. When the extracellular calcium concentration was decreased to the level of a normal intracellular calcium concentration, the toxins had little effect.

During cerebral ischemia, there is a massive shift of calcium from the extracellular fluid into the intracellular space.[22,23] The increase in intracellular calcium is accompanied by a precipitous decrease in the concentration of adenosine triphosphate, the energy source required to drive the ion pumps within the calcium

channel that maintain intracellular calcium homeostasis. This defect augments the increased intracellular calcium concentration, producing calcium overload.

Calcium overload exerts many detrimental effects that can lead to cell catabolism and, ultimately, to cell necrosis. For example, calcium activates the enzyme phospholipase A_2, which releases free fatty acids (FFAs) from membranes.[24] Consequently, anoxic-ischemic neuronal injury is characterized by a large and rapid increase in neuronal FFA content, especially arachidonic acid content. Arachidonic acid can initiate the important sequence of biochemical events that leads to the production of eicosanoids, such as prostaglandins, thromboxanes and leukotrienes.[25] Specific compounds within each of these groups are capable of causing cell damage. Increased FFA levels in neurons also trigger the production of free radicals.[26] Although the role of these oxidative radicals in neuronal injury remains controversial,[27] the potential entropic threat posed by their ability to initiate deleterious biochemical reactions cannot be ignored.

Calcium overload also appears to be related, directly or indirectly, to the delayed, inadequate reperfusion that typically follows anoxia-ischemia. Such hypoperfusion has been associated with myofibrillar contracture and increased vascular resistance.[28]

When considered together, these findings are compatible with the thesis that increased intracellular calcium concentrations play a pivotal role in the events leading to neuronal death after anoxia-ischemia.[24,29] If, indeed, the sequence of events depicted in Figure 1 is valid, interventions that break the cascade at 1 or more points may result in the salvage of cerebral tissue. Using calcium-channel blockers to decrease the intracellular influx of calcium is 1 such intervention; consequently, studies designed to assess the value of calcium-channel blockers in treating patients with acute ischemic stroke seem justified.

Pharmacology

Calcium-channel blockers are a rather nonhomogenous group of drugs, containing derivatives of papaverine, dihydropyridine and piperazine. These drugs have widely differing structures, potencies and tissue-dependent specificites. Their 1 common property is the ability to interfere with an action-potential–induced transmembrane movement of calcium.

The papaverine derivatives, such as verapamil and D-600, have been shown to block contractions of the surgically exposed cat basilar artery. Flunarizine, a piperazine derivative, appears to block contractions in both basilar and internal carotid arteries.[30]

The most potent vasodilators among the calcium antagonists are the 1.4-dihydropyridine substitutes nifedipine and nimodipine, and nimodipine is the more powerful of the 2. These compounds have been shown to block contractions in the canine basilar artery at concentrations that are 10,000 times less than the concentrations of papaverine required to block contractions in the feline basilar artery.[2]

The activity of these agents appears to be tissue-, organ- and, in some instances, species-specific. When administered in clinically relevant doses, nifedipine was more effective in blocking the calcium channels in smooth muscle than in cardiac muscle, and appeared to have little if any effect on pacemaker activity and atrioventricular nodal conduction.[31] Results of other studies indicate that agonist-induced contractions of the basilar arteries in dogs[32] and rabbits[33] can be inhibited by nimodipine, whereas contractions of femoral arteries in these animals are affected to a lesser degree. The differences in tissue specificity have been attributed to variations in the types of calcium channels present in different tissue types, whereas their organ- and, possibly, species-specificity are thought to reflect variations in the distribution of these channels.

Animal models of calcium-channel blocker therapy in ischemia: One well-studied model of ischemic brain damage, the rat preparation by Levine,[34] has recently been used in pharmacologic investigations of calcium-channel blockers. In this model, cell

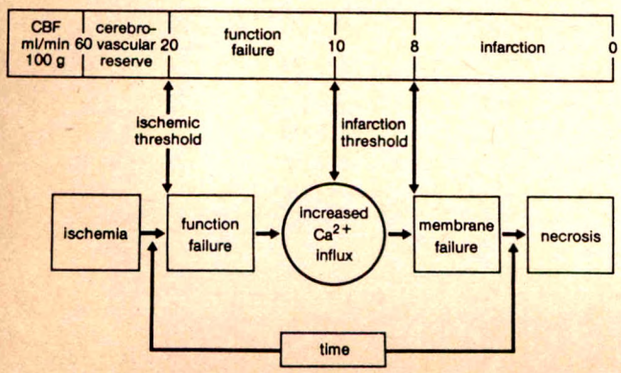

FIGURE 1. The ischemic cascade. Values are approximations obtained from experimental data. CBF = cerebral blood flow.

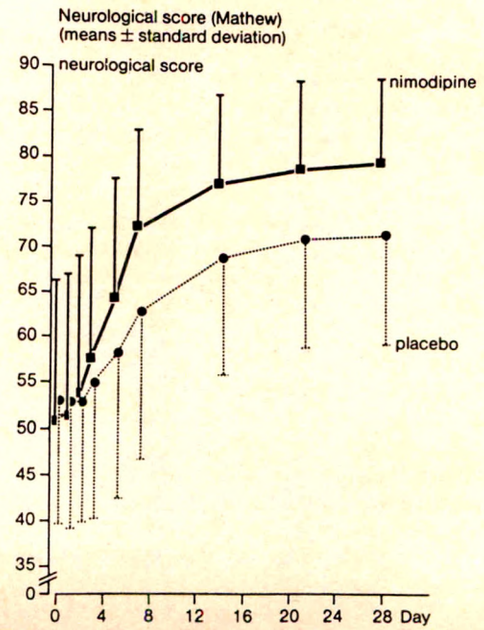

FIGURE 2. Mathew scale neurologic scores for ischemic stroke patients treated with nimodipine (n = 29) or placebo (n = 31).

changes typical of ischemia are produced by intermittently exposing rats to a pure nitrogen environment for several 1-minute intervals during a 40-minute period. Artificial respiration is administered after each interval of oxygen deprivation. Using this model, investigators sought to determine whether flunarizine offers pharmacologic protection against ischemic cell changes.[33] Flunarizine-treated rats had only moderate ischemic cell damage in limited areas, lending support to the hypothesis that ischemic cell necrosis is the result of calcium overload. However, these findings remain to be corroborated by clinical studies.

Animal studies of dihydropyridines have yielded findings similar to those obtained with flunarizine. Treatment with nimodipine was found to prevent impaired cerebral reperfusion after a 7-minute interval of total cerebral ischemia.[35] In a separate study, investigators found that the progressive deterioration evident on electroencephalograms recorded during the later stages of the ischemic and postischemic phases was absent in animals premedicated with nimodipine.[36]

Results of nimodipine treatment in baboons were inconsistent; the drug either increased CBF without affecting cerebral metabolism or it decreased blood flow.[37] The disparity between these and other animal findings is probably traceable to differences in study design and methods because the effect of nimodipine on CBF varied with the type of animal preparation used.

Clinical findings: CBF measurements in volunteers and stroke patients suggest a small overall increase in CBF after nimodipine treatment, with a redistribution of blood flow within the infarcted hemisphere.[38,39] These findings are in agreement with those indicating that stroke patients have increased blood flow in ischemic areas and decreased blood flow in unaffected cerebral areas, whereas hemispheric blood flow remains unaltered.[40]

Nimodipine Clinical Trial

To date, results of only 1 clinical trial evaluating the effects of calcium-channel blocker therapy on the neurologic deficits resulting from acute ischemic stroke are available.[41] Designed as a 1-center, randomized, single-blind, pilot investigation, the study included 60 patients with acute ischemic stroke. Diagnosis was confirmed by a complete neurologic work-up, which included electroencephalogram, lumbar puncture, radioisotope brain scans, and computerized axial tomography scan. All patients were entered into the study within 24 hours of the onset of neurologic symptoms.

Of the 60 patients, 29 were selected for nimodipine treatment, and the remaining 31 were designated as control. All 60 patients received a standard regimen of 10% depolymerized dextran for 5 days. The 29 patients randomized to calcium-channel blocker therapy received additional treatment for 28 days with 120 mg/day of nimodipine administered either orally or, in the case of patients with dysphagia, by nasogastric tube. Heparin therapy (10,000 IU divided between 2 doses) was given subcutaneously for prevention of deep-vein thrombosis. Digitalis, antihypertensives and antibiotics were administered as required, but treatment with vasodilators, steroids and hyperosmolar agents was withheld.

Treated and control groups received comparable supportive care from nurses, physical, speech and occupational therapists, and other members of the hospital staff. Differences between the 2 groups in patient characteristics (for example, mean age, sex, stroke type and risk factors) were not statistically significant.

Therapeutic efficacy was assessed using the Mathew scale for neurologic scoring.[40,42] As shown in Figure 2, pretreatment scores for the 2 groups were similar; however, on Day 8 of nimodipine treatment, the neurologic scores for treated patients began to differ from those for control subjects. This disparity persisted throughout the remainder of the 4-week study, indicating greater recovery of neurologic function in the nimodipine-treated patients compared with those who received dextran therapy alone ($p < 0.0001$).

During the period of observation, both treated and control groups showed minimal decreases in systolic blood pressure; however, in no patient did the decrease herald a deterioration in clinical condition. The differences between the blood pressure readings for the 2 groups were not statistically significant. Mean heart rate increased initially with standard therapy, but decreased during nimodipine treatment. No other clinically relevant adverse effects were noted in either study population.

In summary, animal and clinical findings accrued to date support the theory that calcium influx into cerebral cells during ischemia contributes to cell death. Animal data indicating that calcium antagonists protect neuronal cells from ischemia, together with clinical evidence attesting to improved neurologic function after nimodipine treatment, suggest that calcium-channel blockers offer promise in the management of patients with acute ischemic stroke. It should be noted, however, that the results of 1 single-blind study cannot be considered conclusive and must be confirmed by further investigation. To fulfill this need, double-blind studies of nimodipine therapy in stroke victims are currently underway.

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Role of Calcium Antagonists in Cerebral Arterial Spasm

GEORGE S. ALLEN, MD, PhD

Spasm of the large cerebral arteries at the base of the brain causes delayed ischemic neurologic deficits in approximately 30% of patients after a subarachnoid hemorrhage from an intracranial aneurysm. In vitro chamber studies have shown that both dog and human large cerebral artery segments contract to a variety of vasoactive agents, and the dog and human segments are remarkedly similar in their responses. The source of calcium necessary to initiate contraction was found to be extracellular for large cerebral arteries. In contrast, systemic arteries such as the femoral artery use a bound intracellular pool of calcium for contraction. The calcium antagonists nifedipine and nimodipine were found to selectively inhibit the contractions of large cerebral arteries but not the femoral artery. In vivo experiments demonstrated that both nifedipine and nimodipine, given sublingually, would prevent and reverse cerebral arterial spasm in the dog after a subarachnoid hemorrhage. Nimodipine was found to be more potent, both in the chamber and in the live dog experiments. Nimodipine significantly decreased the occurrence of severe neurologic deficits from spasm alone in a multi-institutional, prospective, double-blind, randomized, placebo-controlled trial. **(Am J Cardiol 1985;55:149B–153B)**

The patient who survives a subarachnoid hemorrhage from an intracranial aneurysm remains at risk during the next 3 weeks because of recurrent hemorrhage and cerebral arterial spasm. Recurrent hemorrhage is effectively treated by clipping the aneurysm. Cerebral arterial spasm is focal or diffuse narrowing of ≥1 of the large arteries at the base of the brain. Such spasm is rarely seen on angiograms taken within the first 96 hours after the hemorrhage. In contrast, it is frequently seen from 4 to 21 days after the hemorrhage. It is now well accepted that delayed (several days after the initial hemorrhage) ischemic neurologic deficits are caused by spasm. The time course of the onset of the neurologic deficits coincides with the time course of spasm seen on angiograms (4 to 21 days after the hemorrhage). The peak incidence for the onset of a neurologic deficit is the ninth day after hemorrhage. The incidence of such delayed neurologic deficits is highest in the group of patients whose initial computerized axial tomography (CAT) scans show large amounts of blood in the basal subarachnoid cisterns. Neurologic deficits are very infrequent in those patients whose initial CAT scans fail to disclose any blood in the basal cisterns. The exact cause of spasm and the chain of events leading to the ischemic neurologic deficit have not been firmly established. A reasonable working hypothesis is that one or more vasoactive substances contained in the blood clots in the basal cisterns interact with the cerebral arteries to cause severe constriction. After some period of severe constriction, there are morphologic changes that take place in the wall of the cerebral arteries, such as swelling and necrosis of the smooth muscle cells. Such morphologic changes in the arteries may cause them to remain narrowed without the continued presence of vasoactive substances. The net result is ischemia to the area of the brain supplied by the vessel in spasm. Approximately 30% of all patients with a subarachnoid hemorrhage will have delayed neurologic deficits from spasm, and half of these patients will either die or be left with severe neurologic deficits.

If the initial event in the development of cerebral arterial spasm is the contraction of the smooth muscle cells in large cerebral arteries, then a drug that inhibits these contractions should prevent both spasm and neurologic deficit. To be effective, such a drug must also cross the blood-brain barrier in order to reach the cerebral arterial smooth muscle cells. Its inhibition should be selective and not affect the contractions of systemic arteries to the extent that severe hypotension occurs.

In Vitro Study of Contractions of Large Cerebral Arteries

We developed a chamber that allowed us to measure the isometric contractions of large cerebral arterial segments. The chamber is designed so that arterial

From the Department of Neurosurgery, Vanderbilt University, Nashville, Tennessee. This study was supported in part by grants from the National Foundation of the March of Dimes, United Cerebral Palsy Research and Educational Foundation and Miles Pharmaceuticals Company (American subsidiary of Bayer).

Address for reprints: George S. Allen, MD, PhD, Department of Neurosurgery, Vanderbilt University, Nashville, Tennessee 37232.

segments 3 to 4 mm in length are placed over 2 stainless steel prongs so that a constant resting tension can be developed and isometric contractions measured. The arterial segments are bathed by buffer, and the temperature is kept constant. Aliquots of vasoactive agents to be tested can be added to the chamber bath and dose-response curves to these agents can be determined from the increase in contractile activity of the segments. Our initial experiment showed that canine basilar and middle cerebral artery segments gave dose-dependent contractions to a variety of agents, including serotonin, prostaglandin $F_{2\alpha}$, prostaglandin A_1, bradykinin, epinephrine and norepinephrine, histamine and potassium chloride.[1] Of all the agents tested, serotonin was found to have the smallest $K_{ED_{50}}$. Next, we demonstrated that cerebrospinal fluid taken from patients several days after a subarachnoid hemorrhage would cause dose-dependent contractions of canine basilar arteries. In contrast, cerebrospinal fluid collected from patients undergoing lumbar myelography had no contractile activity.[2] Most contractile activity in these cerebrospinal fluid samples was shown by paper chromatography in 3 separate solvent systems to be due to serotonin. We carried out a similar series of experiments on cerebral arterial segments from 6 persons obtained within an hour of death at autopsy.[3] The response of the human arterial segments was strikingly similar to that of the canine arterial segments (Fig. 1). The human arterial segments also responded in a dose-dependent fashion to cerebrospinal fluid collected from 2 patients several days after their hemorrhage who had delayed ischemic neurologic deficits and angiographically demonstrated spasm (Fig. 2).

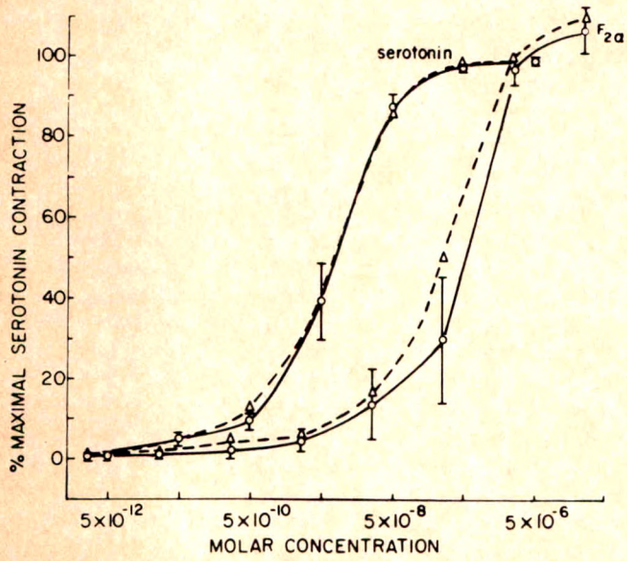

FIGURE 1. Mean cumulative log dose-response curves of human cerebral arteries (**solid lines**) and canine basilar arteries (**dashed lines**) for serotonin and prostaglandin $F_{2\alpha}$. Number of arteries tested are as follows: serotonin on human arteries = 6, $F_{2\alpha}$ on human arteries = 5, serotonin on canine arteries = 4, F_2 on canine arteries = 4. Brackets = standard error of the mean (SEM); 100% response to serotonin = 12.2 g ± 1.6 SEM. Reprinted with permission from *J Neurosurg.*[3]

The results demonstrate that human and canine large cerebral arteries are capable of contracting in a dose-dependent fashion in response to a variety of vasoactive agents. Furthermore, they demonstrate that the canine cerebral arteries are a good model for studying the contractile mechanisms of human cerebral arteries. They also demonstrate that cerebrospinal fluid taken from patients several days after a subarachnoid hemorrhage would cause significant contraction of large cerebral arteries, and that most contractile activity was due to serotonin in the cerebrospinal fluid.

Studies were then carried out with such classic serotonin antagonists as methysergide and cyproheptadine.[2] These serotonin antagonists were not as effective at low concentrations in inhibiting the serotonin-induced contraction of large cerebral arteries. We were initially puzzled by these results. It was recently documented, however, that there are 2 different serotonin receptors, a high affinity 5-HT_1 receptor and a low affinity 5-HT_2 receptor, and we recently showed that canine basilar arteries use the high affinity 5-HT_1 receptor in their contractile response to serotonin.[4] At the present time, there are no known 5-HT_1 receptor antagonists. All of the classic serotonin antagonists have been shown to antagonize the lower affinity 5-HT_2 receptor; this explains their lack of effectiveness on large cerebral artery segments.

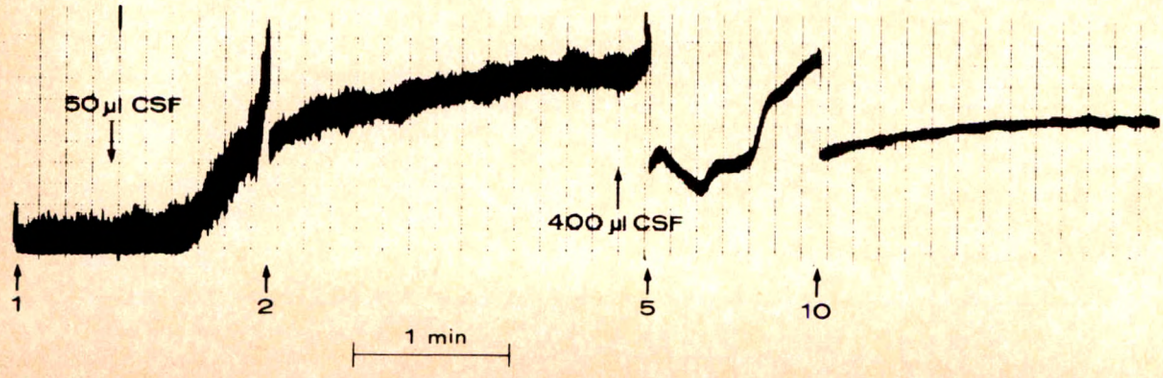

FIGURE 2. Polygraph tracing of isometric contraction of human anterior cerebral artery segment after addition of human cerebrospinal fluid (CSF) obtained 7 days after subarachnoid hemorrhage. Numbers at base of tracing indicate gram tension at full scale reading, and **arrows** at base show when this was changed. **Arrows on tracing** indicate when CSF was added in volumes shown. Reprinted with permission from *J Neurosurg.*[3]

Determination of the Source of "Activator" Calcium for Large Cerebral Arteries

From the available experimental data, it appears that the concentration of free calcium present at the actin and myosin filaments determines the degree of contraction at any given moment. By regulating the amount of intracellular free calcium present at the site of the contractile proteins, the smooth muscle cell is able to regulate the amount of contraction. This "activator" calcium can come from 2 different sources: extracellular calcium or bound intracellular calcium. Van Breemen et al[5] have shown that lanthanum effectively blocks the passage of extracellular calcium into the vascular smooth muscle cell, and, further, that it binds all of the extracellular sites that normally hold calcium. They also showed that norepinephrine, angiotensin and histamine produce 1 contraction after the application of lanthanum to strips of rabbit aorta. After this 1 contraction, no further contraction could be produced regardless of which agent was used. They interpreted this result as showing that norepinephrine, angiotensin and histamine were able to use a common intracellular pool of calcium, which was replaced by extracellular calcium. This replacement was blocked by lanthanum.[5] We[6] repeated this experiment using canine basilar artery segments and serotonin, phenylephrine and prostaglandin $F_{2\alpha}$. We were unable to obtain any contraction after the application of lanthanum with any of these 3 vasoactive agents.[6] Additional experiments demonstrated that the removal of calcium from the bath buffer also prevented most of the contraction obtained with these 3 agents. We concluded that, unlike the rabbit aorta, large cerebral arteries use primarily extracellular calcium as the source of activator calcium. Subsequently, we repeated these experiments using canine femoral arterial segments and determined that they behave much like the rabbit aorta. After the application of lanthanum, a single contraction or a series of decreasing contractions could be obtained. The removal of calcium from the bath buffer did not initially cause much decrease in the amount of contraction obtained with these vasoactive agents.

These results suggested that the newly developed calcium antagonists might selectively block the contractions of large cerebral arteries without affecting the contractions of systemic arteries to the extent that severe hypotension would occur.

The initial experiments were carried out with nifedipine because it was the most potent of the then known calcium antagonist group of drugs.[7] We demonstrated that nifedipine in a dose-dependent fashion inhibits the contractions of the basilar artery to serotonin, phenylephrine and potassium chloride. In contrast, nifedipine at a concentration that effectively inhibited the basilar artery (3×10^{-8} M) did not significantly inhibit the contractions of the femoral artery induced by serotonin and phenylephrine. Potassium chloride contractions were significantly inhibited in the femoral artery by nifedipine. High potassium contractions had been previously shown to induce contractions in a variety of smooth muscle cell preparations by causing an influx of extracellular calcium.[8]

TABLE I Changes in Cross-Sectional Area (radius^2/control radius^2) of Basilar and Ventral Spinal Arteries of Dogs After the Subarachnoid Injection of Blood and Treatment with Nifedipine*

Time of Angiogram (±10 minutes)	% of Control	
	Basilar	Ventral Spinal
Control (n = 3)	100	100
30 minutes after SAH	73 ± 7	50 ± 10
80 minutes after SAH	71 ± 7	48 ± 15
Control (n = 4)	100	100
30 minutes after SAH	52 ± 9	50 ± 10
80 minutes after SAH 30 minutes after nifedipine	133 ± 27	122 ± 17
Control (n = 4)	100	100
30 minutes after SAH 50 minutes after nifedipine	135 ± 21	127 ± 21
Control (n = 4)	100	100
2 days after SAH	57 ± 7	52 ± 9
2 days after SAH 30 minutes after nifedipine	111 ± 8	96 ± 8

* 1 mg/kg of nifedipine placed under the tongue of the dogs.
SAH = subarachnoid injection of 2.5 ml blood. Reprinted with permission from *Neurosurgery*.[9]

In vivo studies were then carried out in dogs.[9] The dogs were sedated with intravenous sodium pentobarbital and intubated; a vertebral artery was then selectively catheterized using a femoral artery approach. A control angiogram of the cerebral circulation was obtained, and then a subarachnoid hemorrhage was produced by inserting a 20-gauge spinal needle into the cisterna magna and injecting 2.5 ml of fresh whole blood from the dog being studied. Subsequent angiograms taken at varying time intervals showed that after the subarachnoid hemorrhage, spasm was produced. Nifedipine dissolved in polyethylene glycol 400 was administered sublingually, and angiograms were taken 30 minutes later. This study demonstrated that nifedipine, at a concentration of 1 mg/kg, was capable of both preventing and reversing the short-term spasm. It was also effective in reversing spasm seen 2 days after the hemorrhage (Table I). The large and consistent effect of nifedipine allowed the results from only 4 dogs in each experimental group to be statistically significant. In addition, the results in each experimental group supported the results of the other experimental groups, and the in vivo results confirmed the earlier in vitro results with nifedipine. Significant hypotension did not occur in the dogs given sublingual nifedipine.

The Bayer Pharmaceutical Company was consulted concerning a clinical trial of nifedipine in patients after a subarachnoid hemorrhage. They suggested that an analogue of nifedipine, now known as nimodipine, might be even more effective on cerebral arteries. We carried out additional in vitro and in vivo studies comparing nimodipine with nifedipine.[10,11] Nimodipine was found to inhibit the serotonin-induced contractions of the canine basilar artery at nanomolar concentrations (Fig. 3). In contrast, even at micromolar concentrations, it had very little effect on serotonin-induced contractions of the canine femoral artery (Fig. 4). Studies were also carried out using human frontal cortex to study the binding of tritiated nimodipine.[12] Nimodipine was found to have a K_i of 0.29 nM and nifedipine a K_i of 1.0

TABLE II Correlation Between Nimodipine's Binding and Its Inhibitory Effect on the Basilar Artery

	H^3 Binding Human Brain Apparent K_i (nM)	Chamber	
		Dog Basilar Artery IC_{50}(nM)	Dog Femoral Artery IC_{50}(nM)
Nimodipine	0.29 ± 0.07	0.20	>10,000
Nifedipine	1.0 ± 0.3	6.2	2,600

nM. The correlation between nimodipine's binding and its inhibitory effect on the basilar artery is striking (Table II). At a concentration of 0.29 nM, one half of the binding sites are occupied by nimodipine; at a similar concentration of 0.20 nM in the chamber, nimodipine has one half of its maximal inhibition of the basilar artery's contractile response to serotonin. In contrast, nifedipine does not have as high an affinity in binding studies and has even less of an effect on the canine basilar artery with an IC_{50} of 6.2 nM. Its effect on the canine femoral artery is also greater than nimodipine's. Subsequent in vivo studies of nimodipine and nifedipine again demonstrated that a sublingually administered dose of 0.28 mg/kg of nimodipine was more effective in reversing angiographic spasm than nifedipine at this same dose. An additional potential benefit of nimodipine is that it is more lipid soluble than nifedipine and therefore might cross the blood-brain barrier more readily.

These results led us to choose nimodipine for a prospective trial in patients who had had a subarachnoid hemorrhage from a ruptured intracranial aneurysm.

Controlled Trial of Nimodipine in Patients After a Subarachnoid Hemorrhage

One hundred twenty-five patients from 5 institutions were enrolled in a prospective, double-blind, randomized, placebo-controlled trial of nimodipine. Each had a subarachnoid hemorrhage from a ruptured intracranial aneurysm.[13] The study was designed as an explanatory trial and not a management trial.[14] The objective was to determine if nimodipine was effective in either preventing or altering the severity of ischemic neurologic deficits caused by spasm. Only patients who were neurologically normal according to study criteria were entered so that the development of the neurologic deficit could be accurately determined. A subarachnoid hemorrhage from the aneurysm had to have occurred within 96 hours before treatment began so that all patients were at risk for spasm. All patients were randomized in a double-blind manner to receive gelatin capsules containing either nimodipine or placebo. The dose of nimodipine was 0.35 mg/kg, rounded to the nearest full 10 mg capsule every 4 hours for 21 days.

If a neurologic deficit developed during the 21-day treatment period, the patient, within 48 hours of the occurrence, underwent a series of diagnostic tests, including CAT scan and intracranial angiography. The neurologic outcome at the end of treatment was classified as normal or severe; there was also an exclusion group termed mild or moderate for those patients with a neurologic deficit that did not meet the definition of severe. Two endpoints were defined for analysis of efficacy: the development of a neurologic deficit from cerebral arterial spasm alone and the severity of the deficit at the end of the treatment period. The following criteria were established before the trial ended: contingency table analysis with Fisher's exact test of significance would be used to examine the 2 endpoints; a two-tailed significance level (p value) <0.05 would be necessary to conclude that nimodipine was effective and the study would be terminated, regardless of the results, after 125 patients were entered.

After the study was completed and the data analyzed, it was found that randomization was effective (patients were well matched). Eight of the 60 patients given placebo either died or still had severe deficits from spasm at the end of treatment (Table III). In contrast, only 1 of the 56 patients given nimodipine fell into the severe outcome category (p = 0.03, Fisher's exact test). This analysis excluded both 5 patients with protocol violations and 4 patients who did not meet the entry criteria. If the 5 patients with protocol violations had been included, the p value would have been 0.02. The conclusion that administration of nimodipine was responsible for this difference in outcome is supported by the following findings: (1) placebo and nimodipine groups were

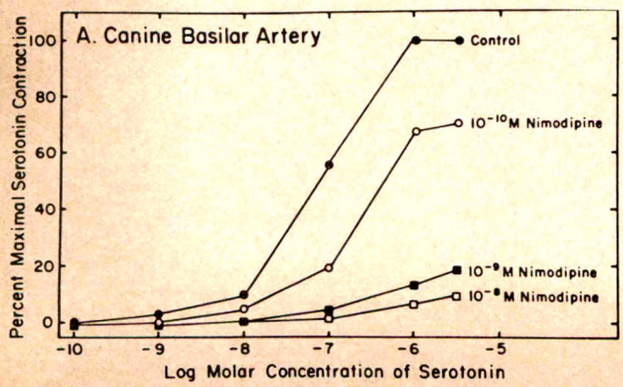

FIGURE 3. Mean cumulative log dose-response curves of canine basilar artery segments to serotonin with various bath concentrations of nimodipine. Reprinted with permission from *Headache*.[11]

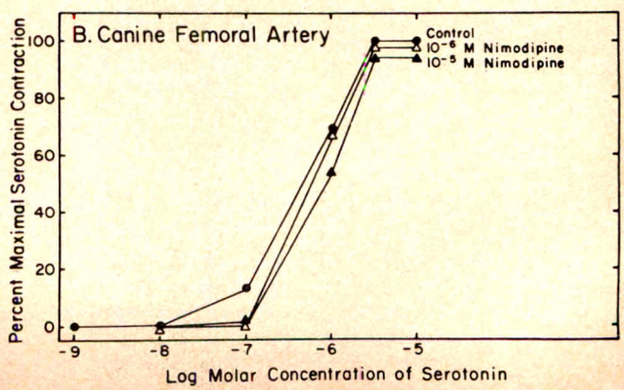

FIGURE 4. Mean cumulative log dose-response curves of canine femoral artery segments to serotonin with various bath concentrations of nimodipine. Reprinted with permission from *Headache*.[11]

similar with respect to every known factor that might have influenced either the development of neurologic deficit from spasm or the neurologic outcome; (2) nimodipine had no apparent adverse effects, and therefore, the double-blind nature of the study was maintained; (3) analysis of preentry CAT scans and angiograms of patients with neurologic deficits from spasm revealed that nimodipine was associated with a significant change in the degree of spasm seen angiographically in patients with large amounts of blood in their basal subarachnoid spaces, (4) nimodipine was present in the cerebrospinal fluid of the patients; and (5) the results of similar previous experiments in animals were consistent with the results of the clinical trial.

In this trial, nimodipine, however, did not prevent the occurrence of deficits from spasm alone. Rather, its effect was analogous to the shifting of a dose-response curve to the right. The number of patients in both treatment groups who had deficits from spasm alone was not significantly different. In contrast, there was a significant difference in the severity of the deficit between nimodipine and placebo groups. It is reasonable to suggest from these results that the dosage of nimodipine administered produced an important effect but not a maximal one. Concern about the safety of nimodipine, which had not previously been given to patients with subarachnoid hemorrhage, led us to choose a dosage that might not be maximally efficacious, according to our experiments in dogs. Because there were no serious adverse effects from nimodipine, it seemed reasonable to conduct a second explanatory trial using a higher dosage. This study is now in progress at 25 institutions in North America. Patients are receiving 30, 60 or 90 mg every 4 hours in a random manner. We hope to confirm the results of our initial trial and show a dose-dependent relation between nimodipine and the occurrence and severity of neurologic deficits from cerebral arterial spasm alone.

Several questions remain to be answered. The results of the first trial with nimodipine need to be confirmed. The oral administration may not always be the best route of administration, and trials are underway in Europe with an intravenous preparation of nimodipine as well as a topical application of a nimodipine solution to be used when cerebral artery surgery is performed. The optimal dosage of nimodipine has not been established, but we should know more after our second trial. The mechanism of action of nimodipine remains open to question. The basis for the clinical trial was nimodipine's inhibition of large cerebral artery contractions. We know from binding experiments, however, that nimodipine binding sites occur in brain tissue. It may be that, at least in part, the improved clinical results seen in patients after a subarachnoid hemorrhage are due to nimodipine's effect on neuronal tissue. Finally, nimodipine and nifedipine are both substituted 1,4 dihydropyridines. There are other calcium antagonists with different chemical structures, such as verapamil and diltiazam, that appear to bind to different sites on the calcium channels on human frontal cortex than nimodipine does.[12] The clinical efficacy of these drugs in cerebral arterial spasm remains to be determined.

TABLE III Patients Who Had Deficits From Spasm: Neurologic Outcome at End of 21-Day Treatment Period

Placebo	Nimodipine
Normal	
n = 6	n = 8
Mild to Moderate	
n = 2 Patient 1. 3/5 left hemiparesis 2. Disoriented to year	n = 4 Patient 1. Disoriented to city 2. 3/5 left arm 3. Disoriented to city, 4/5 right leg, mild aphasia 4. 4/5 left hemiparesis
Severe	
n = 8 Patient 1,2,3. Death* 4. Coma, decerebrate 5. No verbal response 0/5 left hemiparesis 6. Severe aphasia, 2–3/5 quadraparesis 7. 0–1/5 left hemiparesis 8. Moderate aphasia, 2/5 right hemiparesis	n = 1 Patient 1. Death

* All patients who died had severe deficits immediately before death.
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Raynaud's Phenomenon: Pathophysiologic Features and Treatment with Calcium-Channel Blockers

CRAIG R. SMITH, MD, and RICHARD J. RODEHEFFER, MD

Raynaud's phenomenon may be associated with severe pain, functional disability and digital infarction, particularly in patients with underlying vascular disease. The pathophysiologic features of Raynaud's phenomenon are complex although vasospasm contributes to the production of digital ischemia in most cases. Calcium-channel blockers have been shown to produce arteriolar vasodilation and an increase in peripheral blood flow. They have been used to treat patients with Raynaud's phenomenon in several prospective, randomized, double-blind, placebo-controlled trials. Low doses of verapamil were ineffective but both diltiazem and nifedipine produced subjective improvement in 60 to 90% of cases. Objective measures of digital blood flow were not improved. Patients without underlying vascular disease responded more readily to therapy than patients with scleroderma. Adverse effects were uncommon and seldom necessitated discontinuation of therapy. These data suggest that nifedipine and diltiazem provide effective short-term improvement in symptoms for most patients with Raynaud's phenomenon.

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Raynaud's phenomenon is characterized by the abrupt development of digital pallor or cyanosis in response to cold exposure or stress.[1,2] Ischemic symptoms such as parathesias and numbness often accompany the pallor, last as long as the stimulus is present and are followed by hyperemia, pain and throbbing of the digits. The color changes are usually sharply circumscribed, involve 1 or more fingers and may be asymmetrical. The condition may produce functional disability, digital atrophy, ulceration or gangrene, particularly in patients with underlying vascular disease. Raynaud's phenomenon may also be part of a generalized process involving the feet, ear lobes and visceral vessels of the lung, kidney or heart.

Pathophysiologic Features

The pathophysiologic features of Raynaud's phenomenon are complex (Fig. 1).[3] From Poiseuille's law it can be deduced that there are 3 mechanisms that may decrease digital blood flow: decreased perfusion pressure, increased blood viscosity or decreased luminal area of the digital artery.[4,5] Each of these mechanisms may occur individually or in combination and each may be caused by specific anatomic or functional abnormalities. Decreased perfusion pressure may be caused by systemic hypotension or proximal vascular occlusion. Increased blood viscosity may be caused by increased plasma fibrinogen, increased platelet adhesion or decreased red cell deformability.[6–9] Most often decreased flow is induced by a decrease in the luminal area of the digital artery. Decreased luminal area is caused either by anatomic vascular occlusion, vasospasm or both. Anatomic luminal occlusion is the hallmark of patients with scleroderma. These patients have intimal and advential fibrosis, but they may also have diffuse small fibrin thrombi that further impair digital flow.[10] Patients with systemic lupus erythematosis, rheumatoid arthritis and polyarteritis nodosa also have luminal obstruction due to focal vasculitis or thrombosis.

Arterial and arteriolar vasospasm is a normal response to cold exposure or stress. Vasospasm may be caused by a central adrenergic response or to changes in local mediators that control vascular smooth muscle tone. Recent data suggest that cold increases the α-adrenergic responsiveness of the digital vessels by increasing release of norepinephrine, decreasing norepinephrine degradation and possibly increasing receptor sensitivity.[11] An increase in adrenergic vasomotor tone has long been thought to be a factor in Raynaud's phenomenon. Perhaps patients with Raynaud's phenomenon have a more aggregated response making them more likely to have spasm or severe spasm.

Local mediator abnormalities including diminished prostacyclin or increased thromboxane production have also been suggested as causes for vasospasm in Raynaud's, but conclusive evidence for these abnormalities

From the Divisions of Internal Medicine and Clinical Pharmacology, the Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Address for reprints: Craig R. Smith, MD, Harvey 402, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, Maryland.

TABLE I Double-Blind Clinical Trials of Calcium-Channel Blockers in Raynaud's Phenomenon

Report	Patients (n)	Drug	Dose (mg)	Duration (weeks)	Attack Frequency Decreased	Subjective Improvement	Objective Improvement
Kinney et al[16]	17	Verapamil	40–80 qid	2	No	No	No
Vayssairat et al[17]	26	Diltiazem	60 tid	2	Yes	Yes	. . .*
Kahan et al[21]	30	Nifedipine	20 tid	2	Yes	Yes	. . .*
Smith and McKendry[22]	17	Nifedipine	10 qid	2	Yes	Yes	No
Rodeheffer et al[23]	15	Nifedipine	20 tid	2	Yes	Yes	No

* Not measured.
qid = 4 times daily; tid = 3 times daily.

is lacking.[12] In fact, a preliminary report suggests that thromboxane is not of pathogenic importance in Raynaud's phenomenon.[13] Serotonin responsiveness has also been studied in an in vitro system. Cutaneous vascular smooth muscle strips from patients with scleroderma had an increased contractile response to serotonin compared with vascular smooth muscle strips from normal subjects. On the basis of these data, further studies of the influence of serotonin and the responsiveness of the vasculature to serotonin seem indicated.

Calcium-Channel Blockers

Both in vitro and in vivo experiments have demonstrated that calcium-channel blockers decrease vascular smooth muscle tone and relieve arterial vasospasm. Drug-induced vasodilation causes a decrease in peripheral vascular resistance and an increase in peripheral blood flow.[14] Moreover, calcium-channel blockers inhibit, in vitro, norepinephrine-induced vasospasm of rabbit and human peripheral arteries and veins.[15] Because of these unique properties, several investigators have studied the effectiveness of calcium-channel blockers in patients with Raynaud's phenomenon (Table I).

Kinney et al[16] conducted a double-blind, prospective, crossover trial in 17 patients given verapamil 40 to 80 mg 4 times a day for 2 weeks. They measured therapeutic efficacy by diary tabulation of attack frequency, subjective evaluation of overall effectiveness and digital systolic pressures. There was no significant difference between placebo- and verapamil-treated patients in the number or severity of attacks, the subjective evaluation of effectiveness or the mean digital systolic pressure during cold exposure. In this study, small doses of verapamil were used and most patients had underlying vascular disease. Further study is necessary to determine if larger doses would be more effective and to determine if patients without underlying vascular disease would be more responsive.

Vayssairat et al[17] studied diltiazem in 26 patients with Raynaud's phenomenon. Diltiazem, 60 mg, was given 3 times a day for 2 weeks in a double-blind, placebo-controlled prospective trial. This study demonstrated an improvement in patients' subjective assessment of disability and in the frequency of attacks. Symptoms decreased 17% during placebo treatment compared with 51% during diltiazem treatment and the number of vasospastic attacks decreased by 6.5 and 64%, respectively ($p < 0.05$). No objective evidence of improvement in digital blood flow was demonstrable. The investigators concluded that diltiazem was effective therapy for patients with Raynaud's phenomenon.

Matoba et al[18] have also investigated diltiazem. They conducted an open-label trial in 17 men with vibration-induced Raynaud's. Diltiazem, 30 mg, was given 3 times a day for 6 weeks. Effectiveness was assessed by subjective patient reports, skin temperature recovery

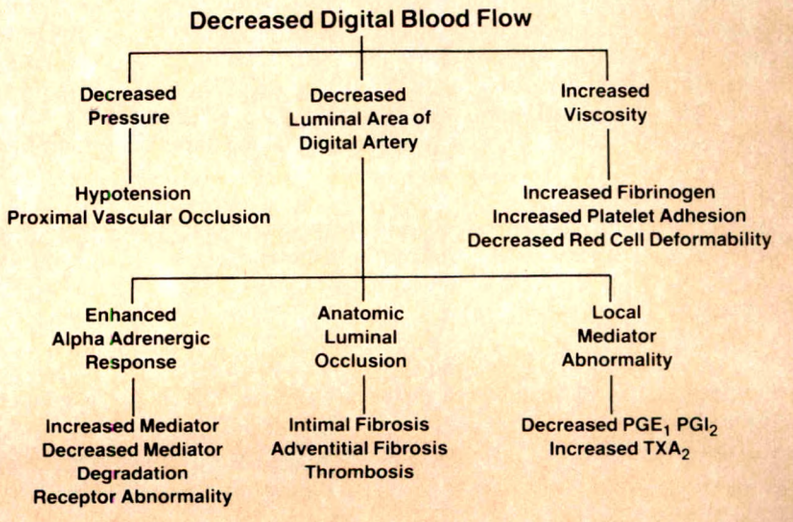

FIGURE 1. Pathophysiologic features of Raynaud's phenomenon.

TABLE II Patient Assessment of Therapeutic Efficacy

Subjective Assessment	Nifedipine n (%)	Placebo n (%)
Moderated or marked improvement	9 (60)*	2 (13)
Minimal improvement, no change or worse	6 (40)	13 (87)

* p = 0.02, Fisher's exact test.

times and digital sensory tests. Matoba observed significant ($p < 0.05$) improvement in skin temperature recovery times and sensory tests. Most notably, 69.6% of the patients judged diltiazem "effective" and no adverse effects were reported. Matoba concluded that diltiazem was effective in the long-term management of vibration-induced Raynaud's phenomenon.

Most recently, a randomized, prospective, double-blind trial of diltiazem has been reported by Kahan et al.[19] They studied 16 patients with scleroderma, rheumatoid arthritis, systemic lupus erythematosis and idiopathic Raynaud's phenomenon. Symptom severity was measured using a 10 point scale. When all 16 patients were evaluated, mean attack frequency decreased from 18.9 per 2-week period with placebo to a 12.6 with diltiazem ($p < 0.05$). Attack severity was rated 6.2 with placebo and 4.2 with diltiazem ($p < 0.05$). Patients with idiopathic disease appeared to respond more dramatically than those with an underlying systemic disease.

Three studies have assessed the effects of nifedipine in patients with Raynaud's phenomenon. Kahan et al[20] reported the preliminary results of a controlled, prospective trial in 16 patients. Nifedipine, 20 mg, was given as a single oral dose on 2 consecutive days. Vasospasm was induced by hand immersion in cold water before and at the first and sixth hour after nifedipine and placebo administration. Nifedipine delayed the onset of digital vasospasm in 14 of the 16 patients compared with placebo. A long-term, open-label study of the effectiveness of nifedipine, 20 mg 3 times daily, was then conducted with 10 patients. There was a decrease in the mean number of digital vasospastic attacks per week from 29.5 to 4.3 and 4 of the 10 patients were entirely free from attacks. Kahan et al[21] subsequently published the results of a randomized, prospective, placebo-controlled, double-blind, crossover trial in 30 patients treated with nifedipine, 20 mg 3 times daily for 2 weeks. The number of vasospastic episodes decreased 90.1% for patients with idiopathic Raynaud's phenomenon, 78.6% for patients with systemic lupus erythematosis and 64% for patients with scleroderma. These differences were statistically significant compared with placebo, suggesting that nifedipine was effective therapy for most patients with digital vasospasm, but more so in those with idiopathic Raynaud's phenomenon.

Smith and McKendry[22] conducted a prospective, double-blind, crossover trial comparing placebo with nifedipine, 10 mg 4 times daily for 2 weeks, in 17 women with idiopathic Raynaud's phenomenon, scleroderma and systemic lupus erythematosis. Effectiveness was assessed by diaries, subjective evaluation and skin temperature recovery times after cold exposure. Severity and global effectiveness were measured with 10 cm visual analogue scales in which a score of 10 indicated the greatest severity or effectiveness. The frequency of attacks decreased from 2.5 ± 0.4/day with placebo to 1.3 ± 0.3/day with nifedipine. The severity of attacks decreased from 5.8 ± 0.6 with placebo to 3.4 ± 0.5 for nifedipine, and effectiveness improved from 1.3 ± 0.6 to 5.3 ± 0.8. No improvement was measurable in skin temperature recovery times.

Finally, Rodeheffer et al[23] conducted a placebo-controlled, double-blind trial of nifedipine in the treatment of patients with Raynaud's phenomenon. Patients with digital vasospasm caused by thoracic outlet syndrome, vibratory trauma, large vessel atherosclerosis, thromboangiitis obliterans and polyarteritis nodosa were excluded from the trial. The trial consisted of 4 study periods: a placebo run-in period lasting 2 weeks followed by 2 treatment periods of 2 weeks duration each, separated by a 1-week washout period. During the treatment periods, patients received either nifedipine, 20 mg 3 times a day, or placebo. Several measurements were taken to determine the drug effectiveness. These included the patient's global assessment of drug effectiveness on a 5 point scale, diaries in which the patients tabulated the frequency and severity of their vasospastic episodes on a daily basis and digital artery systolic pressures, taken while patients were lying on a thermal blanket at 30 and 15°C. The trial was conducted during cold weather months.

The frequency of Raynaud's attacks per 2 weeks decreased from 14.7 episodes with placebo to 10.8 episodes with nifedipine ($p < 0.05$). This response was more pronounced in patients with idiopathic Raynaud's phenomenon. The patients' overall assessment of the effectiveness of nifedipine versus placebo therapy was also significantly different. Moderate or marked subjective improvement occurred in 60% of the patients with nifedipine and in only 13% with placebo, $p = 0.02$ (Table II). Despite improvement in the number of vasospastic episodes and marked improvement in the patients' global assessment of therapy, no changes could be detected in digital perfusion pressures when nifedipine and placebo were compared.

The results of these clinical trials indicate that during nifedipine treatment many patients have a decrease in the frequency of vasospastic attacks and a moderate or marked alleviation in their symptoms. However, there was variability in the response to therapy, with some patients having no response at all. Patients without underlying vascular disease appeared to respond better whereas patients with scleroderma appeared to do less well. The reason for the difference in individual responses to nifedipine cannot be determined from the data, but may be due to variation in the severity of vasospasm, variation in extent of fixed anatomic narrowing of the digital arteries, presence of active vasculitis or other as yet uncharacterized variables associated with the presence of an underlying systemic disease.

In these studies, calcium-channel blockers were conveniently administered and well tolerated. The most common adverse effects were flushing, mild headache, a sensation of light-headedness and ankle edema. Because these symptoms were usually mild and transient, they should not limit the clinical utility of these drugs in patients with Raynaud's phenomenon.

The lack of correlation between subjective alleviation of symptoms and objective evidence of improvement in digital blood flow was a consistent finding in these studies. The methods used to measure digital flow included digital sphygomomanometry, venous occlusion plethysmography and skin temperature recovery times. The reason for the failure of these methods to detect improvement is not clear. It may be that blood flow was improved during the tests but the methods were not sensitive enough to detect it, or that blood flow was not improved during the application of the tests. In each study blood flow measurements were performed after a cold challenge; in 2 studies the hands were placed in ice cold water for 20 seconds[20,21] and in 1 study patients were asked to lie on a cooling blanket at 15°C for 20 minutes.[23] These stimuli provoked digital vasospasm in most patients. Although it is possible that the blood flow measurement techniques used were insensitive, it is also possible that the magnitude of the stimuli used during the objective tests was too great to be reversed by nifedipine or diltiazem. Because the magnitude of the stimuli used during the tests was probably far in excess of the magnitude of the stimuli these patients were exposed to in daily living, it may be that calcium-channel blockers were effective in blocking the vasospastic response to mild or moderate stimuli but not to severe stimuli.

In summary, 5 independent, double-blind, controlled clinical trials have shown that short-term treatment with nifedipine or diltiazem provides symptomatic relief in many patients with Raynaud's phenomenon. Further clinical studies are needed to determine the site of drug action, the dose-response relation, the effectiveness of long-term therapy and the predictors of clinical responsiveness.

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Influence of Calcium-Channel Blockers on Platelet Function and Arachidonic Acid Metabolism

JAWAHAR L. MEHTA, MD

Available data indicate that platelet function and arachidonic acid metabolism are important factors in hemostasis and regulation of vascular tone. Plasma membrane and intracellular mobilization of calcium ions are intimately related to platelet activation and release of platelet contents. Release of arachidonic acid from membrane phospholipids as well as subsequent synthesis and release of vasoconstrictor thromboxane A_2 are also regulated by movement of calcium ions. Adenosine 3′:5′-cyclic phosphate in turn controls levels of free calcium ions in platelets and regulates calcium-dependent reactions. Slow-channel calcium blockers, such as verapamil, diltiazem and nifedipine, inhibit platelet activation in vitro, and decrease platelet adhesion intravascularly. These agents have also been shown to decrease platelet nucleotide release and thromboxane A_2 generation. Some preliminary data suggest that calcium blockers also increase generation of vasodilator and platelet antiaggregant prostacyclin, which could contribute to decrease in platelet function. These effects of calcium blockers on platelet function and arachidonic acid metabolism could contribute in part to their efficacy in patients with ischemic heart disease.

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Arterial thrombosis involves a complex interaction between blood vessels and blood components, primarily platelets. It is natural, therefore, that platelet inhibitory agents are used in disease states characterized by evidence of arterial thrombosis.

Upon injury to the vascular intima, platelets adhere to the subendothelial layers and the process of platelet activation is initiated. After the shapes change, platelets undergo release reaction during which intracellular contents like adenosine diphosphate (ADP) and thromboxane A_2 are released. Circulating platelets attach to the adhering platelets, resulting in the formation of platelet aggregates. Other blood components including white blood cells, red blood cells, thrombin and fibrin are incorporated in the platelet aggregate. Platelet activation also promotes coagulation cascade and influences vasomotor activity, resulting in arrest of bleeding. After hemostasis and repair of endothelium, platelet thrombus disaggregates. However, abnormalities in the physiologic interrelations between platelets and vessel walls, such as platelet hyperactivity or persistent endothelial injury, may result in formation of intraluminal thrombi, decrease in blood flow, tissue ischemia and injury, and perhaps atherosclerosis as well. Thus, thrombosis and atherosclerosis may be considered an extension of the normal hemostatic mechanism. In the last decade, it has become apparent that platelet-vessel wall interactions are mediated in large part by products of arachidonic acid metabolism. These products include prostaglandins, prostacyclin, thromboxane A_2, hydroxy-fatty acids and leukotrienes.

Various platelet reactions as well as arachidonic acid metabolism have been shown to depend on calcium mobilization. In this report, I review evidence for the involvement of calcium in platelet activation, and discuss the effects of drugs that interact with calcium-dependent platelet functions.

Calcium and Platelets

Several studies show that calcium ions and cyclic nucleotides are interrelated factors in the coupling of extracellular messages to intracellular responses such as platelet aggregation and the release reaction.[1–3] Such stimuli as adenosine diphosphate (ADP) and ionophore A23187 cause calcium ions to be liberated from the platelet membrane-binding sites and the dense tubular system into the platelet cytoplasm. This results in platelet shape change and reversible aggregation. High concentrations of agonists cause platelet contractile activity, which results in extrusion of platelet granular

From the Division of Cardiology, University of Florida College of Medicine and the Veterans Administration Medical Center, Gainesville, Florida.

Address for reprints: Jawahar L. Mehta, MD, Department of Medicine, University of Florida, Box J-277, JHMHC, Gainesville, Florida 32610.

ıtents (release reaction) and irreversible aggregation. ıtelet release reaction and irreversible aggregation dependent on intracellular calcium mobilization. As idence, deuterium oxide, which interferes with cal- ım mobilization, and chlortetracycline, which chelates racellular calcium, inhibit platelet shape change, ease reaction and aggregation caused by ADP.[4] There several intracellular storage pools of calcium, such the dense tubular system, α-granules, dense bodies d mitochondria. The mitochondrial calcium is obably not a major factor in platelet activation. Ac- ation of different processes requires calcium from ferent sources; for example, calcium released from e surface membrane is involved in platelet shape ange, and the larger intracellular pool of calcium in e dense tubular system and dense bodies is mobilized cause release reaction (Fig. 1).

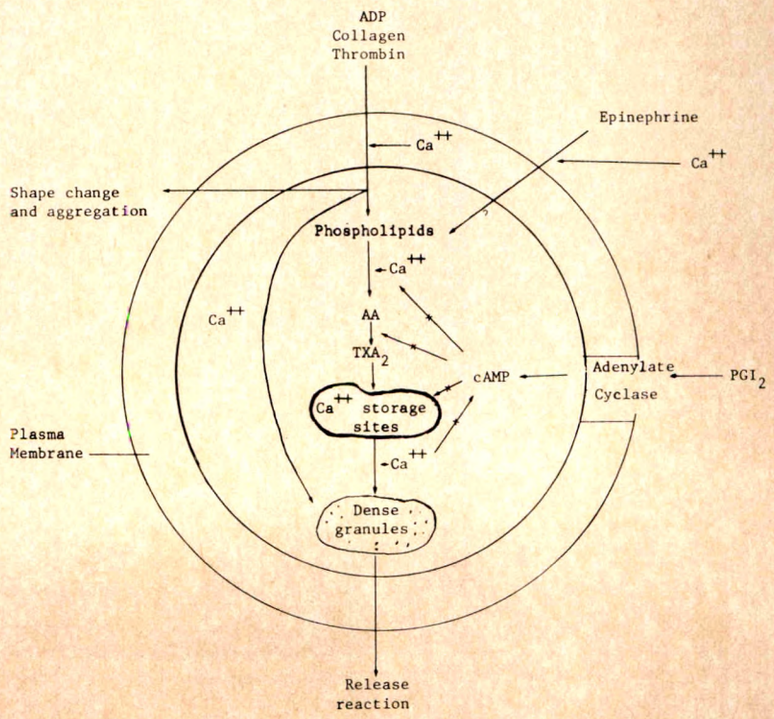
After the initial stimulation of platelets with ADP, rombin and collagen, platelet membrane permeability creases with resultant influx of calcium from the ex- acellular medium, which may also participate in bsequent platelet activation. Increase in membrane rmeability occurs after the earlier release of calcium om the plasma membrane. ADP, thrombin and col- gen can, however, activate platelets in the presence ethylenediaminetetraacetic acid (EDTA), which elates extracellular calcium, suggesting that influx calcium might be the consequence rather than the use of platelet activation.

In contrast to ADP, thrombin and collagen, epi- phrine induces platelet aggregation without shape ange and secretion. In the early stages of epineph- ne-induced aggregation, there is uptake of calcium om the extracellular medium by platelets.[5] As evi- nce, epinephrine-induced aggregation is blocked by rapamil-induced blockade of calcium uptake. In the second stage of platelet activation, epinephrine also causes intracellular calcium mobilization. Thus, epinephrine-induced platelet aggregation requires an initial influx of calcium to cause internal mobilization (Fig. 1). Part of the proposed calcium-induced calcium release is due to stimulation of phospholipases by calcium. In the later stages of activation, binding of extracellular calcium to plasma membrane occurs, which is essential for platelet aggregation. This calcium binding is also necessary for interactions between clotting factors and platelet membrane.

The intracellular mobilization of calcium has several effects, including disruption of the microtubules, contraction of the calcium-dependent contractile system, fusion of the membranes of dense bodies, platelet prostaglandin generation and release of the platelet-activating factor. Of these, prostaglandin generation has received considerable attention in the last decade.

Upon platelet activation, arachidonic acid is cleaved from membrane phospholipids by action of phospholipases C and A_2. Both of these enzymes require calcium for their activity. Free intracellular calcium is a major regulatory step in the generation of arachidonic acid, which is metabolized in the platelets to cyclic endoperoxides (PGG_2 and PGH_2) and then to prostaglandins E_2, D_2, $F_{2\alpha}$ and thromboxane A_2. Thromboxane A_2 is a very potent vasoconstrictor and platelet pro-aggregant. It has been proposed that thromboxane A_2 also facilitates transport of calcium from storage sites into the cytoplasm. Adenosine 3′:5′-cyclic phosphate (cyclic AMP) promotes reuptake of calcium into the storage sites and reverses the aggregation process. Thromboxane A_2 decreases cyclic AMP and may be considered an amplifier for intracellular calcium release.

Recent studies suggest that many of the effects of calcium ions are mediated by the intracellular cal-



GURE 1. Postulated interaction between calcium a^{++}), cyclic AMP (cAMP) and arachidonic acid (AA) etabolism. PGI_2 = prostacyclin; TXA_2 = thromboxane 2.

TABLE I Verapamil and Platelet Thromboxane A_2 Generation (Thromboxane B_2 ng/10^8 Platelets)

Verapamil Concentration	ADP		Epinephrine		AA	
	2 μM	n	55 μM	n	1 mM	n
0	6.29 ± 0.56	5	7.65 ± 0.62	4	80.8 ± 4.2	9
0.5 μg/ml	5.65 ± 0.32	4	7.31 ± 0.32	4	79.6 ± 6.7	5
5 μg/ml	4.21 ± 0.31*	4	8.08 ± 0.56	4	80.0 ± 4.3	5
25 μg/ml	...	...	4.20 ± 0.32†	4	63.5 ± 4.0*	5
50 μg/ml	1.14 ± 0.20†	4	1.40 ± 0.29†	4	60.1 ± 3.2†	5
250 μg/ml	...	...	...	...	17.8 ± 2.1†	3
500 μg/ml	...	...	...	...	5.8 ± 0.5†	3

Data expressed as mean ± standard error of the mean.
* $p < 0.05$.
† $p < 0.02$.
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n = number of experiments.

cium-binding protein calmodulin.[6] Calmodulin itself is not active, but it forms an active complex with calcium, the calmodulin-calcium complex. Calmodulin is indeed present in platelets[7] and inhibitors of calmodulin inhibit platelet aggregation and release reaction.[8]

Calcium, Cyclic AMP and Platelet Activation

The relation between calcium and cyclic AMP is important in the regulation of platelet activation. Cyclic AMP controls levels of free calcium in platelets and regulates calcium-dependent reactions by several mechanisms (Fig. 1). Calcium inhibits adenylate cyclase and causes a decrease in cyclic AMP. Platelet aggregation inhibitors like prostacyclin increase intracellular cyclic AMP, whereas prostaglandin endoperoxides and thromboxane A_2 inhibit cyclic AMP accumulation caused by prostacyclin and prostaglandin E_1. Agents that increase cyclic AMP levels generally inhibit thromboxane A_2 synthesis. Cyclic AMP inhibits mobilization of arachidonic acid from membrane phospholipids.[9] Cyclic AMP accumulation inhibits conversion of arachidonic acid to thromboxane A_2[10] as well. There is some evidence that cyclic AMP also prevents release of ionized calcium from the storage granules.

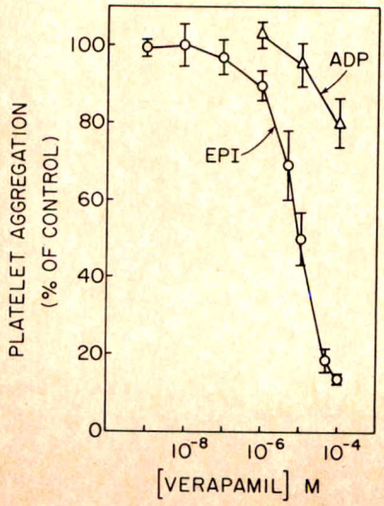


FIGURE 2. Effects of various concentrations of verapamil on platelet aggregation induced by epinephrine (EPI) and adenosine diphosphate (ADP). Reprinted with permission from *Am J Physiol.*[18]

Calcium-Channel Blockers and Platelet Activation

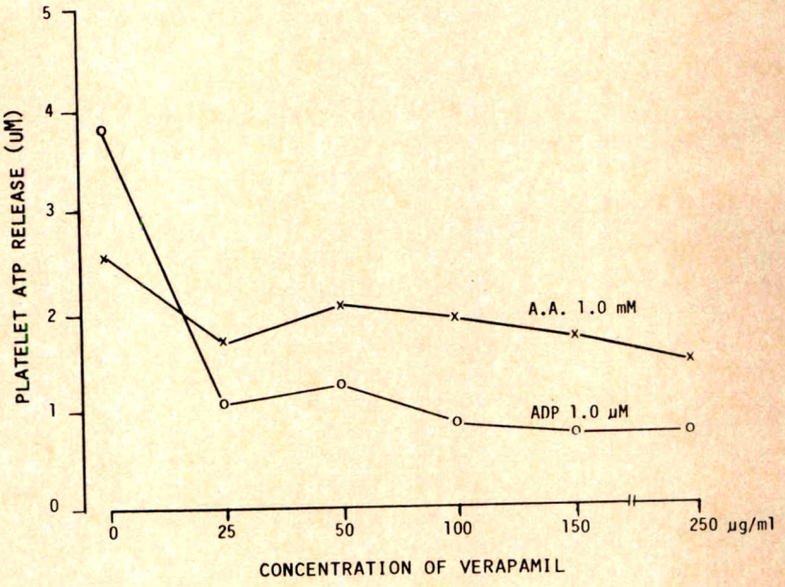
Increase in intracellular calcium, which initiates the contractile process, can be due to influx of calcium or to intracellular mobilization of calcium. A group of drugs commonly known as calcium-channel blockers are now available. These agents have variable effects in different biologic tissues; however, all calcium-channel blockers share the common property of inhibiting calcium entry. In low concentrations, calcium-channel blockers inhibit transmembrane flux of calcium.[11] On the other hand, these agents at similar or higher concentrations interfere with intracellular mobilization of calcium.[12,13]

Chierchia et al[14] showed that verapamil inhibits human platelet aggregation in concentration-dependent fashion. Epinephrine and collagen-induced aggregation was inhibited more than ADP-induced aggregation. Similar observations were made by Owen,[5,15] Ikeda,[16] Mehta[17] and their co-workers. Relatively low concentrations of verapamil block transmembrane calcium flux in response to epinephrine,[5,15] probably mediated through platelet α_2 receptors.[18] In contrast, ADP, collagen and ionophore A23187-induced platelet activation (caused by mobilization of calcium from membrane and intracellular stores) is inhibited at much higher concentrations (Fig. 2). Verapamil also inhibits platelet nucleotide release and thromboxane A_2 generation (Fig. 3, Table I). In normal subjects[16] and in patients with coronary artery disease,[14] platelet aggregation and circulating platelet aggregates are decreased with the use of verapamil. It has been postulated that some of the in vivo metabolites of verapamil may contribute to its antiplatelet effects.[16,17]

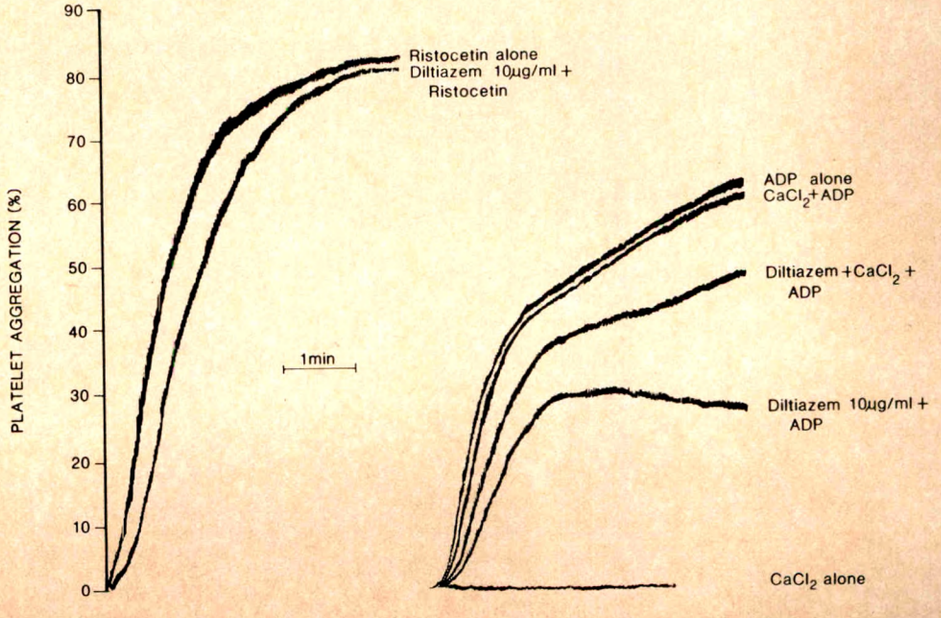
Effects of 2 other calcium-channel blockers, diltiazem[19,20] and nifedipine,[21] on platelet function have also been examined. These agents, like verapamil, inhibit platelet aggregation induced by ADP, epinephrine and ionophore A23187 in supratherapeutic concentration (≥500 ng/ml). Exogenous calcium blunts the platelet inhibitory effects of these agents. Ristocetin-induced platelet activation, which is calcium-independent, is not affected; this suggests that the inhibitory effects of these agents depend on calcium mobilization (Fig. 4). Some of the in vivo metabolites of diltiazem were recently shown to exert platelet aggregation inhibitory effects,[21]

; in high concentrations. Diltiazem's weak but defi-
e inhibitory effects on platelet α_2 adrenoceptors[22]
y also be important in the effects of this and related
npounds on platelet activation.

As discussed earlier, in vitro platelet activation is
ibited by these agents at supratherapeutic concen-
tions. On the other hand, administration of usual
es of verapamil and diltiazem is associated with
rease in indexes of platelet activation.[14,16] We believe
t platelet aggregation induced by a single stimulus
vitro may not reflect the in vivo state, because it is
hly unlikely that stimuli are present in vivo in
regatory concentrations. On the other hand, it is
ely that small amounts of several stimuli act on
telets in combination. To examine this possibility,
examined the effects of different platelet stimuli in
nbination on platelets. Indeed, the combination of
stimuli, each in a very small concentration, was capable of inducing complete and irreversible platelet aggregation.[20] In this "potentiated" platelet aggregation system, very small amounts of diltiazem (50 to 100 ng/ml) significantly inhibited platelet activation (Fig. 5). Platelet thromboxane A_2 generation in response to combination of stimuli was also markedly reduced by diltiazem (Table II). This was especially evident when the "potentiated" system involved calcium ionophore A23187. Once platelet aggregation had been initiated, the concentrations of calcium-channel blocking agents required to inhibit aggregation were very high (Fig. 5). Nifedipine, another calcium-channel blocking agent, also reduced platelet aggregation and thromboxane A_2 synthesis when platelets were stimulated with ionophore A23187 plus ADP or epinephrine. This inhibition was evident at concentrations of 100 to 500 ng/ml.



GURE 3. Effects of verapamil on platelet adenosine
phosphate (ATP) release. Data shown are means of 3
parate experiments. AA = arachidonic acid.



IGURE 4. Absence of any significant
ffect of 10 µg/ml of diltiazem on ris-
ocetin-induced platelet aggregation
eft). Exogenous calcium chloride
$CaCl_2$) (3 µM) reversed effects of dil-
azem on adenosine diphosphate
ADP)-induced platelet aggregation.
his concentration of $CaCl_2$ did not by
self induce aggregation and did not
otentiate effects of ADP (**right**). Re-
rinted with permission from *J Lab Clin Med.*[20]

TABLE II Effect of Diltiazem on Platelet Aggregation and Thromboxane A_2 Release Induced by Ionophore A23187 Plus Adenosine Diphosphate or Epinephrine

	Thromboxane B_2 (ng/10^8 platelets)	Platelet aggregation	%
Ionophore A23187 (subthreshold concentrations) alone	0.45 ± 0.05	10 ± 5	5
ADP (subthreshold concentrations) alone	0.17 ± 0.02	5 ± 6	5
Ionophore A23187 + ADP	11.37 ± 1.21	69 ± 7	5
Diltiazem (0.05–0.10 μg/ml, 0.1–0.2μM) + ionophore A23187 + ADP*	4.37 ± 0.51‡	25 ± 6‡	5
Ionophore A23187 + ADP + diltiazem (0.5 μg/ml, 1.1 μM)†	13.41 ± 1.74	70 ± 8	3
Epinephrine (subthreshold concentrations)	0.35 ± 0.04	8 ± 4	5
Ionophore A23187 + epinephrine	14.41 ± 2.02	75 ± 8	5
Diltiazem (0.1–0.5 μg/ml, 0.2–1.1 μM) + ionophore A23187 + epinephrine*	5.79 ± 1.05‡	45 ± 8‡	5
Ionophore A23187 + epinephrine + diltiazem (5 μg/ml, 11.1 μM)†	12.46 ± 1.89§	68 ± 7	4

Summary of several experiments. Data expressed as mean ± standard error of the mean. Sequence of diltiazem and aggregating agents was as mentioned above.
* Diltiazem was incubated with platelets for 1 minute before addition of ionophore A23187.
† Diltiazem added after the potentiation of aggregation had begun (see arrows on Figure 3).
p values compared with ionophore A23187 + ADP or epinephrine.
‡ $p < 0.01$.
§ $p < 0.05$.
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These studies indicate that calcium-channel blocking agents have important inhibitory effects on platelet activation mediated by calcium, especially when a variety of stimuli are used in combination. Inhibition of α_2 receptors by calcium-channel blockers may also contribute to the platelet inhibitory effects of these agents.

Another potential mechanism by which calcium-blocking agents may reduce platelet activity is stimulation of prostacyclin release. In an interesting study in dogs, Kai et al[23] correlated the peripheral vasodilator effects of the calcium-channel blocker verapamil with increases in plasma levels of 6-keto-$PGF_{1\alpha}$, a stable metabolite of prostacyclin. Pretreatment of dogs with indomethacin reduced the effects of verapamil on peripheral vascular resistance and plasma levels of 6-keto-$PGF_{1\alpha}$, suggesting that the vasodilation caused by verapamil was mediated in part by the prostaglandin system. We have examined the effects of diltiazem on prostacyclin release in fresh human umbilical vein rings by incubating them with diltiazem followed by treatment with prostaglandin substrate arachidonic acid. This caused a marked increase in prostacyclin release in the supernatants.[24] The magnitude of increase in prostacyclin release, measured as 6-keto-$PGF_{1\alpha}$, was dependent on the concentration of diltiazem, and was inhibited by cyclo-oxygenase blocker indomethacin (Fig. 6). The mechanism of increase in prostacyclin by calcium blockers is not clear, but it is possible that the inhibition of vascular thromboxane A_2 by mechanisms similar to those in the platelets may have diverted cyclic endoperoxides to the prostacyclin pathway. Increase in prostacyclin, regardless of the underlying mechanism, could contribute to the decrease in platelet activity seen in man after administration of verapamil or diltiazem.

Pumphrey et al,[25] from the Mayo Clinic, have provided additional direct evidence for inhibition of platelet activation by calcium-channel blockers in dogs with prosthetic arterial graft.[25] Groups of dogs were treated with placebo, verapamil, dipyridamole or nifedipine. The platelet deposition on the proximal anastomosis site, proximal graft, mid graft, distal graft and distal graft anastomosis site was quantitated. The

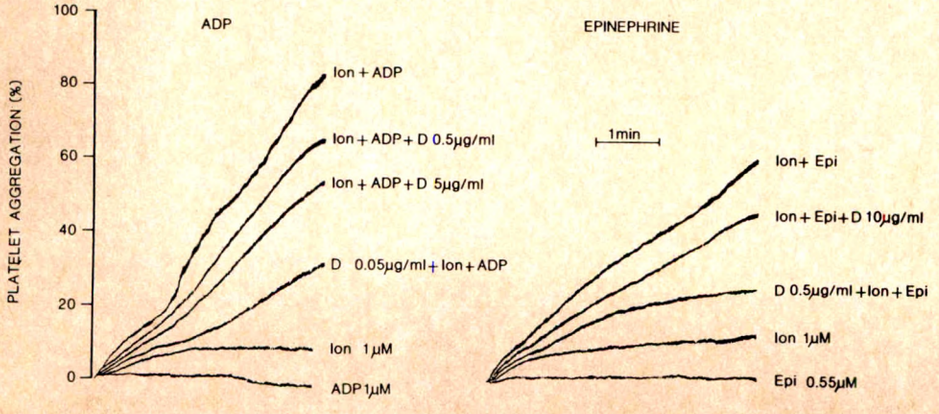
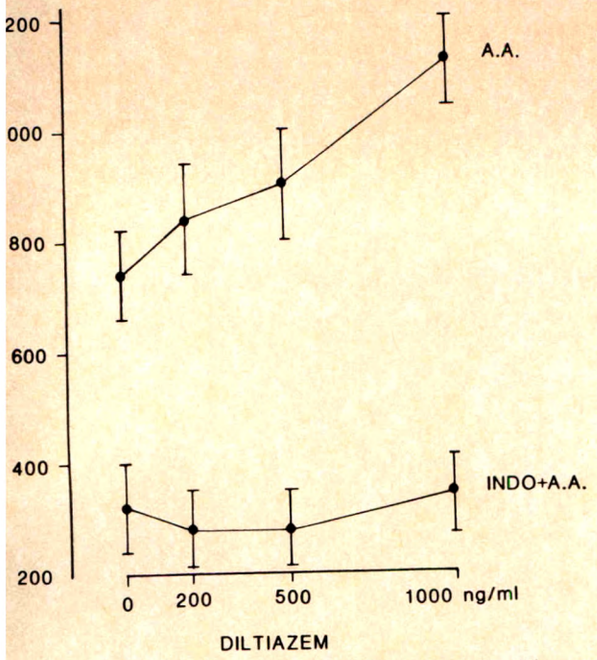


FIGURE 5. Diltiazem and ionophore A23187-induced potentiation of adenosine diphosphate (ADP)-stimulated platelets (**left**) and epinephrine-stimulated platelets (**right**). ADP, epinephrine (Epi) and ionophore A23187 (Ion) were used in subthreshold concentrations. Small concentrations of diltiazem (D) (0.05 to 0.5 μg/ml) added to platelets before ionophore A23187 potentiation of inhibition. In contrast, very large concentrations of diltiazem were required once the potentiation had begun. Reprinted with permission from *J Lab Clin Med.*[20]



GURE 6. Stimulation of prostaglandin (PGI_2) release by diltiazem asured as 6-keto-$PGF_{1\alpha}$, stable hydrolysis product of PGI_2, in vascular g supernatants. Increase ($p < 0.02$) in PGI_2 release was dose-dendent (200 to 1,000 ng/ml of diltiazem). Pretreatment of umbilical n rings with indomethacin (INDO) inhibited ($p < 0.01$) control (buffer diluent for diltiazem) as well as diltiazem-associated increase in PGI_2 ease. Data are summary of 7 different experiments. Data are exssed as mean + standard error. AA = arachidonic acid.

atelet deposition on the graft as well as on the distal aft site was significantly inhibited by dipyridamole would be expected (Fig. 7). Both verapamil and nidipine caused similar and equipotent inhibition of latelet deposition on the prosthetic grafts.

In summary, available data indicate that intracellular calcium concentrations influence arachidonic acid metabolism, cyclic AMP and eventual platelet activity. Calcium-channel blocking agents inhibit platelet activation, cyclic nucleotide release and thromboxane A_2 generation. These phenomena are more readily apparent when low concentrations of multiple platelet stimuli are used in combination. Enhancement of prostacyclin release by calcium blockers may be an additional mechanism of inhibition of platelet activation. These platelet inhibitory effects of calcium-channel blocking agents may contribute to their therapeutic efficacy in man.

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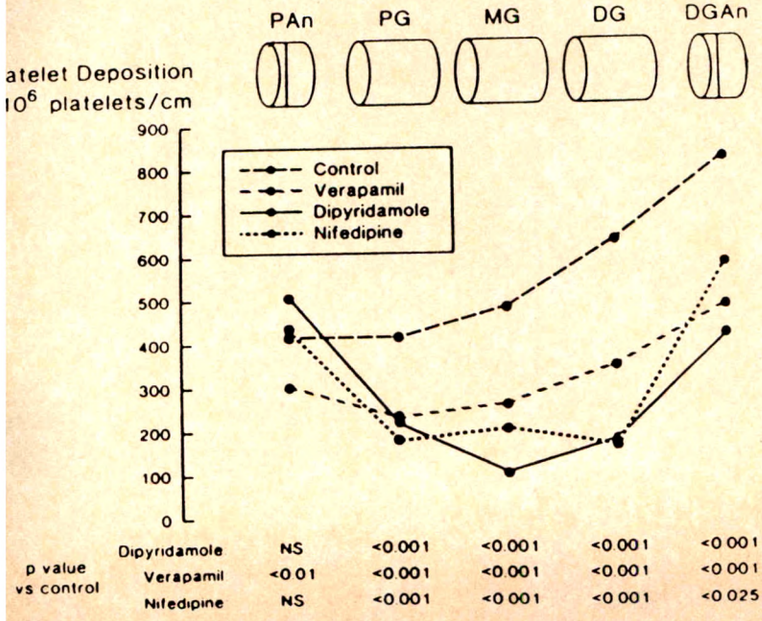

FIGURE 7. Distribution of platelet deposition on polytetrafluoroethylene grafts after 3 hours of perfusion (median values, platelet count × 10^6/cm) and effect of treatment with oral dipyridamole (100 mg in 24 hours before study), intravenous verapamil (7.5 μg/kg/min) and nifedipine (4 μg/kg/min). DG = distal graft; DGAn = distal anastomosis; MG = mid graft; PAn = proximal anastomosis; PG = proximal graft. Reprinted with permission from *Am J Cardiol.*[25]

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Modification of Experimental Atherosclerosis by Calcium-Channel Blockers

WILLIAM W. PARMLEY, MD, STEVEN BLUMLEIN, MD, and RICHARD SIEVERS, BS

The process of atherosclerosis, although not completely understood, is being clarified. A unifying hypothesis holds that the initial event is endothelial injury, followed by platelet aggregation and release reactions. This leads to smooth muscle cell migration into the intima and replication, with subsequent secretion of elastin, collagen and glycosaminoglycans (which binds lipids). Several animal studies have shown that calcium plays an important role in this process. Many drugs with diverse properties can inhibit experimental atherosclerosis. These drugs appear to reduce intracellular calcium. The calcium-channel blockers nifedipine, diltiazem and verapamil, which decrease intracellular calcium, also protect animals from experimental atherosclerosis. The relevance of these animal models to human atherosclerosis is uncertain, and there are very few studies concerning regression of atherosclerosis by interfering with calcium fluxes. Further studies will be needed to clarify these points.

(Am J Cardiol 1985;55:165B–171B)

Atherosclerosis and its consequences continue to be the major cause of death in the United States. It appears to develop over much of the lifetime of a patient, and its development is related to well-known risk factors, especially heredity, hyperlipidemia, hypertension, cigarette smoking and diabetes mellitus.

Over the past several years, multiple studies have documented that increased calcium content of the arterial wall appears to enhance the process of atherosclerosis. Decrease in arterial wall calcium content by a number of pharmacologic agents can ameliorate the development of atherosclerosis in a number of different animal models. More recently, the calcium-entry blockers have demonstrated their ability to modify the atherosclerotic process. This report briefly reviews the role of calcium in the development of atherosclerosis and discusses the data that demonstrate that calcium-entry blockers can attenuate the atherosclerotic process in experimental models.

Pathogenesis of Atherosclerosis

Although the process of atherosclerosis is still not completely understood, a number of major advances have been made in understanding the various processes that are part of this pathologic development.[1–3] Although there is still some disagreement, the fatty streak that appears in children is the probable precursor of the atherosclerotic fibrous plaques that develop later in life. The fatty streak is in part associated with the migration of monocytes (macrophages) and smooth muscle cells through the endothelial layer, which then take up lipid, forming foam cells. The macrophages and smooth muscle cells contain lipids primarily in the form of cholesterol and cholesterol ester. It is probable that much of the lipid within fatty streaks comes from the plasma, although the lipids may be hydrolyzed and reesterified once taken up by cells.

One unifying hypothesis of the pathogenesis of atherosclerosis holds that the initial precipitating step is injury to the endothelium. This can be caused by a number of processes, including mechanical injury, hypercholesterolemia, homocysteinemia and immune injury, among others. Over time, fibrous plaques appear; they are markedly increased and protrude into the lumen. The plaque consists primarily of an accumulation of smooth muscle cells laden with lipid, primarily cholesterol and cholesterol esters. The cells are also surrounded by lipid, collagen, elastic fibers and glycosaminoglycans. The cells and extracellular matrix form a fibrous cap that covers a larger, deeper deposit of extracellular lipid intermixed with cell debris.

The precise sequence of events in the formation of this plaque is not totally clear. It is probable that injury

From the University of California, San Francisco, California. This study was supported in part by a Grant-in-Aid from Don and Susan Schleicher.

Address for reprints: William W. Parmley, MD, University of California, Moffitt 1186, San Francisco, California 94143.

TABLE I Effects of Calcium-Altering Agents on Experimental Atherosclerosis

Investigator	Animal Model	Drug	Mechanism Postulated	Result
Whittington-Coleman and Carrier[4]	Cholesterol-fed rabbits were given oral reserpine, guanethidine or a reserpine analogue	Reserpine, reserpine analogue, guanethidine	Decreased binding of calcium at the cell membrane and elastic tissue	Fat deposition, calcium content and intimal lesions in the aorta were decreased
Whittington-Coleman et al[5]	Rabbits were fed a normal or cholesterol diet with or without intraperitoneal propranolol	Propranolol	Propranolol may have direct action on some metabolic process involving calcium in the vascular wall; the hypotensive property of propranolol prevents further complication of the process	Propranolol decreased the severity of aortic plaques and decreased aortic calcium levels
Morrison et al[6]	Rats fed a normal or cholesterol diet with or without intraperitoneal propranolol	Chondroitin sulfate A	Unknown, not due to lowering of serum cholesterol	Chondroitin sulfate A prevented aortic lesions without lowering serum cholesterol
Rosenblum et al[7]	Rabbits fed cholesterol, vitamin D and nicotine with or without subcutaneous EHDP	EHDP	If arterial calcification is inhibited, so are the other morphologic changes in the arteries	EHDP normalized hypercalcemia and decreased calcification and plaque formation in medium sized arteries; serum lipid levels unchanged
Potokar and Schmidt-Dunker[8]	Oral diphosphonates given to rats after oral vitamin D-induced aortic and renal calcification	Diphosphonic acids	Diphosphates may affect cell permeability to calcium and may affect calcium dependent processes in the cell; treatment prevents in vitro crystallization of hydroxyappatite and so inhibits aortic calcification	Diphosphonates decreased calcification in aortas and kidneys
Chan et al[9]	Rabbits fed cholesterol with or without thiophenes	Thiophenes	Decreased formation of calcium phosphates in arteries; decreased lipid and connective tissue accumulation and decreased cell proliferation due to low CA^{++} and low $PO_4^{=}$; low Ca^{++} and $PO_4^{=}$ may be due to action on adenyl cyclase-cAMP system	Thiophenes normalized the increased calcium level seen in cholesterol-fed rabbits and inhibited atherosclerosis
Wartman et al[10]	Rabbits fed cholesterol for 11 weeks, then normal chow with or without subcutaneous Mg EDTA	Mg EDTA	Mg EDTA decreases extracellular calcium causing an increased PTH level; PTH affects collagen and elastin	Mg EDTA caused plaque regression and decreased aortic collagen and elastin
Kramsch & Chan[11]	Rabbits fed a cholesterol diet with EHDP and/or colcimid	EHDP, colcemid	Cell proliferation and mobility was decreased; secretion of connective tissue proteins was decreased; calcium deposition in elastica and cholesterol binding to elastin protein are decreased	Treatment normalized the increased serum calcium level seen in cholesterol-fed rabbits; aortic accumulation of lipids, calcium, collagen, elastin and glycosaminoglycans were decreased
Kramsch et al[12]	Macacque monkeys fed cholesterol with or without lanthanum or diphosphonates	Diphosphonates, lanthanum	Same as above[11]	Treatment decreased or prevented gross and microscopic atherosclerosis and decreased aortic cholesterol, collagen, elastin and calcium

Kramsch et al[13]	Rabbits fed cholesterol with or without lanthanum	Lanthanum	Lanthanum displaces and replaces calcium on cell membranes and so inhibits calcium-dependent cellular and extracellular responses involved in the atherosclerotic process	Lanthanum decreased or prevented gross and microscopic atherosclerosis; decreased aortic cholesterol, collagen, elastin and calcium; decreased cholesterol, calcium and polar amino acids in elastin
Henry and Bentley[14]	Rabbits fed cholesterol with or without nifedipine	Nifedipine	Nifedipine decreases calcium accumulation in arterial walls and so decreases atherosclerotic lesion formation	Nifedipine decreased aortic cholesterol levels and plaque formation
Ginsberg et al[15]	Rabbits fed cholesterol with or without diltiazem, lanthanum, or flunarizine	Diltiazem, lanthanum, flunarizine	Blockade of calcium influx	All 3 drugs decreased lipid deposition in the aorta but not in the intramural coronary arteries
Rouleau et al[16]	Rabbits fed cholesterol with or without lanthanum or verapamil (oral and subcutaneous)	Verapamil, lanthanum	Verapamil may act by affecting calcium-dependent cellular process, decreasing the shear stress on the arterial endothelium, inhibiting platelet function, some other process	Oral plus subcutaneous verapamil inhibited aortic atherosclerosis

cAMP = cyclic adenosine monophosphate; EDTA = ethylenediaminetetraacetic acid; EHDP = ethane-1-hydroxy-1, 1-diphosphonate; PTH = parathormone.

to the endothelium always permits the development of such a lesion. With the loss of the endothelial barrier, platelet aggregation at the site of injury occurs, followed by the release of platelet-derived growth factor, which leads to the migration of smooth muscle cells from the the media to the intima, and subsequent smooth muscle cell mitosis. These smooth muscle cells secrete elastin, collagen and glycosaminoglycans. Glycosaminoglycans and elastin have a marked propensity to bind low-density lipoproteins, which may be important in the extracellular deposition of lipids during lesion formation. Over time the lesion may develop into a so-called complicated lesion, which is the late state of a fibrous plaque, characterized by hemorrhage, calcification, cell necrosis and mural thrombosis. This latter lesion is frequently associated with occlusion of the involved artery.

Role of Calcium in Atherosclerosis

The role of calcium in this process is a potentially important one. It should be remembered that normally there is an approximately 10,000-fold concentration gradient for calcium, when comparing the high levels in plasma to the low intracellular levels. During any kind of cell injury with membrane damage, the movement of calcium from the outside of the cell to the inside is a common occurrence, and increased calcium concentration can be demonstrated in all damaged tissue. The atherosclerotic plaque is no exception; extensive calcification is observed in these lesions. Even before this extensive influx of calcium, however, there is evidence that increased calcium in the arterial wall may accompany the process of atherosclerosis, at least experimentally. When present in increased amounts, calcium may damage cells by a number of processes, including the depression of mitochondria, with a decrease in the formation of high energy adenosine triphosphate. Presumably, decreases in high energy phosphates lead to the loss of cellular structure and function. In addition, calcium activates various enzymes, which may also be deleterious to cellular function.

Calcium has been implicated in a number of the steps related to the process of atherosclerosis. This includes aggregation of platelets, release of platelet-derived growth factor, smooth muscle cell replication, lipid binding to macromolecules and protein synthesis, to mention just a few. It is reasonable to suppose, therefore, that decrease in the influx of intracellular calcium might have a beneficial role in decreasing the degree of atherosclerosis (Table I).

In this regard, it has been appreciated for some time that catecholamines increase intracellular calcium as part of their effect on receptors. It seems reasonable to expect, therefore, that a decrease in the effects of cathecholamines might tend to decrease vascular calcium. Whittington-Coleman and Carrier,[4] for example, studied the effects of reserpine, 0.1 mg/kg/day, a reserpine analog, or guanethidine, 1 mg/kg/day (each capable of depleting tissue catecholamine), on the development of aortic atherosclerosis in rabbits. Rabbits were fed a 2% (by weight) cholesterol diet for a period

of 10 weeks. Blood lipid levels were unchanged by the 3 drugs. In general, a mild decrease or no significant change occurred in blood pressure. Analysis of the aorta demonstrated a significant decrease in aortic tissue calcium, and a decrease in the degree of atherosclerosis.

Additional studies were carried out by these investigators[5] on the same animal model with propranolol, a β-adrenergic blocker. Results also showed that the calcium content of the aortas of the treated animals was less than that of the control animals fed the high lipid diet. Similarly, the atherosclerotic lesions were less severe than those of the control group. These data further support the notion that catecholamines or increased calcium entry (or both), or intracellular release, may play an important role in the atherosclerotic process, and that inhibition of the cathecholamine effects may be partially protective.

A number of studies have evaluated substances that share the ability of being capable of decreasing the degree of calcification of the aorta, but otherwise differ markedly. Morrison et al[6] studied young adult rats in whom a high lipid diet and hypervitaminosis D led to the development of severe lesions in the coronary arteries and aorta. When the diet was supplemented with chondroitin sulfate A (1%), lipid-containing coronary lesions were markedly decreased. There was no decrease in plasma or liver lipid levels in the animals who had protection. Chondroitin sulfate A has been noted to inhibit the deposition of calcium in the connective tissue of rats.

Using a hypervitaminosis D, nicotine and hypercholesterolemic diet in the rabbit, Rosenblum et al[7] noted the effectiveness of disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP) in preventing atherosclerosis. EHDP inhibited arterial calcification and development of lipid plaques, although it had no effect on serum cholesterol and triglyceride levels. EHDP also inhibited the vitamin D-induced hypercalcemia. Although there was a decrease in the severity of lesions in medium-sized arteries, there was little effect in the aorta. As a group, the diphosphonates are effective inhibitors of a number of different types of pathologic calcification and presumably work in this model by decreasing the amount of intracellular calcification which occurs in the arterial wall.

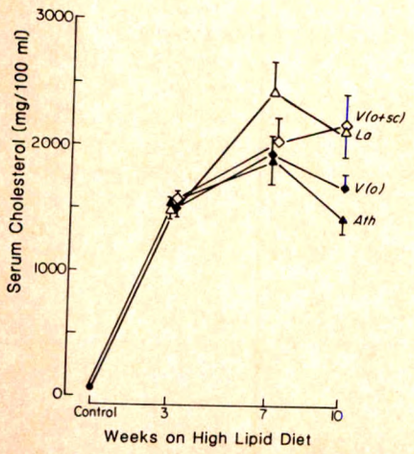

FIGURE 1. Average serum cholesterol levels in each group before (control) and after 3, 7 and 10 weeks on cholesterol-rich diet. Ath = atherosclerotic control; La = lanthanum; V(o) = oral verapamil; V(o + sc) = oral + subcutaneous verapamil. Reproduced with permission from *JACC.*[16]

Additional studies by Potokar and Schmidt-Dunker[8] showed that 3 diphosphonic compounds were able to inhibit the vitamin D-induced calcification of aortas and kidneys in rats. These compounds were chosen because of their ability to prevent in vitro crystallization of hydroxyapatite. In vivo, they also proved to be effective in inhibiting aortic calcification. In fact, selection of the compounds by their in vitro effectiveness was reasonable guidance for their effects in vivo.

Chan et al[9] studied the effect of thiophene compounds. These compounds have marked hypocalemic and hypophosphatemic effects in rats, and in tissue culture inhibit spontaneous and parathyroid-induced bone resorption. An apparent mechanism of action is an inhibition of calcium transfer out of bone. In rabbits fed high lipid diets, all of the thiophene compounds tested normalized an increased serum calcium level, although there was no effect on cholesterol levels. In the aorta, the compound inhibited all aspects of the atherosclerotic process, as determined morphologically and biochemically. There was no bone resorption noted in the treated groups. The close correlation between decrease in calcium deposition in the aorta and decrease in lesions strongly argues for the role of calcium in the atherosclerotic process. Certainly, these drugs do not work by affecting cholesterol levels. Wartman et al[10] have indicated that treatment with the calcium chelator ethylenediaminetetraacetic acid (EDTA) also inhibited and regressed plaque formation in rabbits with dietary-induced atherosclerosis.

Kramsch and Chan[11] also studied EHDP and colcemid in rabbits on a high lipid diet. Although each drug alone was somewhat effective, the combination of EHDP and colcemid virtually stopped the atherosclerotic process. It is possible that the beneficial effects of colcemid may be explained by its ability to disrupt microtubules. Like colchicine and vinblastin, colcemid binds to tubule subunits and disrupts the microtubular assembly. This may suppress proliferation and mobility of cells, as well as the ability for endocytosis and secretion of connective tissue proteins, possibly also of glycosaminoglycans. Because both drugs decreased elevated serum and arterial calcium contents in rabbits, this may be the common mechanism of action.

After initial studies in rabbits, studies were undertaken in monkeys to evaluate the effect of agents that inhibit arterial calcium deposition. Kramsch et al[12,13] showed that the diphosphonates and lanthanum were effective in decreasing arterial wall calcium and the degree of atherosclerosis. Because the rabbit has been criticized as a model of atherosclerosis, the extension of these studies to monkeys is important in demonstrating the same process in relation to calcifying agents.

It was noted that aortas from monkeys treated with diphosphonates or lanthanum, a calcium antagonist, contained smaller amounts of collagen, elastin, cholesterol, calcium and deoxyribonucleic acid (DNA) than the aortas from untreated animals. Lanthanum attaches to cell membranes and displaces calcium from the membranes, thus decreasing migration of calcium intracellularly.

Effects of Calcium-Entry Blockers in Experimental Atherosclerosis

With the increasing use of calcium-entry blockers in cardiology, it was therefore natural to evaluate the effects of these agents on experimental atherosclerosis. Three studies have been published to date using nifedipine, diltiazem or verapamil as the calcium-entry blocker.

Henry and Bentley[14] studied the effects of nifedipine on the process of atherogenesis in rabbits fed a high lipid diet. Nifedipine was given orally (40 mg/day in divided doses). Measurements of arterial pressure showed only transient changes after the oral administration of 20 mg of nifedipine. Otherwise, arterial pressures were the same in the 2 groups of animals. Similarly, the plasma cholesterol levels were the same, approximately 1,900 mg/100 ml. In the animals on the diet only, 40% of the aorta was covered with Sudan IV stained lesions, whereas in the nifedipine-treated rabbits only 17% was covered. Similarly, the cholesterol concentration in aortic tissue was decreased by nifedipine, from 47 to 29 mg/g of protein.

Ginsberg et al[15] evaluated the effects of diltiazem (103 mg/kg/day), lanthanum and flunarizine on aortic and coronary atherosclerosis of rabbits fed a 2% cholesterol diet for 10 weeks. All 3 drugs decreased lipid deposition in the aorta from 52% of the endothelial surface (control) to about 37%. Of interest was the fact that no agent suppressed atherogenesis in the intramural coronary arteries (the epicardial coronary arteries were normal in the control as well as treated animals).

In our own studies,[16] we used verapamil, another calcium-entry blocker. Rabbits were divided into 5 groups. One group was fed a control rabbit chow, and the other groups were fed an atherogenic diet containing 3% soy bean oil and 0.5% cholesterol (by weight). In order to assess the relative effect of lanthanum in our model, we gave 1 group atherogenic chow containing an average of 35 mg/kg of lanthanum trichloride daily. The low-dose verapamil group was fed an atherogenic chow containing an average of 8 mg/kg of verapamil daily. The second group had the same oral dose, but in addition had 0.25 mg/kg of verapamil given subcutaneously twice daily. The increase in serum cholesterol level is shown for the various groups in Figure 1. Note that there was an increase in all groups to a fairly high level by 3 weeks and that there was no essential difference between groups when they were killed at 10 weeks. Specifically, verapamil and lanthanum did not decrease serum cholesterol levels. In fact, the lowest level was found in the atherosclerotic control group.

At the end of 10 weeks, the rabbits were killed, the aortas removed and stained with Sudan IV. A representative aorta from each of the 5 groups is shown in Figure 2. From right to left, the aortas are those of a normal animal fed a regular diet, a control atherosclerotic animal fed a high lipid diet, the lanthanum-treated group, the low dose verapamil group (orally only) and, at the far left, the high dose group that was given both oral and subcutaneous verapamil. Note the significant decrease in atherosclerosis in the high dose verapamil-treated group, as compared with the control group.

Results from all animals are shown in Figure 3, in which the percentage of the aortic surface that was lipid-stained is plotted as a function of the serum cholesterol level. Results are presented as the mean ± standard error of the mean, and demonstrate that the serum cholesterol levels were the same in all groups of animals. There was a significant decrease in the percent involvement of the aorta from 75% in the atherosclerotic controls to 25% in the high dose verapamil-treated group. The percentage of aorta that was lipid-stained tended to be lower in the low dose verapamil and lanthanum groups than in the atherosclerotic control rabbits, but these differences were not statistically significant. Despite what appears to be a relatively high dose of verapamil given to these animals, it should be noted that the serum verapamil levels in the high dose group was quite low (12 ng/ml) compared with clinical standards (70 to 200 ng/ml). The distribution of cholesterol and triglycerides among very low density, in-

FIGURE 2. Representative aortas from different groups of rabbits showing surface area involved with atherosclerosis. From left to right: oral + injected verapamil (V[o + I]), oral verapamil (V[o]), lanthanum-treated (La), control atherosclerotic (C) and normal (N). Sudan IV stain. Reproduced with permission from *JACC.*[16]

termediate density, low density and high density lipoproteins was not different in the different groups of animals.

The fact that verapamil and nifedipine are distinctly different calcium-channel blockers, but have similar effects on the development of atherosclerosis, strongly supports the notion that the mechanism responsible for their salutary effects is related to their ability to reduce intracellular levels of calcium.

We removed papillary muscles from the hearts of the animals we studied, and measured their intrinsic contractile performance in a myograph. Contrary to previous reports,[17] we did not find a decrease in the intrinsic contractility of papillary muscles removed from the atherosclerotic animals. We did find, however, a slight decrease in maximum velocity of shortening in the group of animals treated with the high dose verapamil. Because these studies were conducted relatively soon after the subcutaneous administration of verapamil, it was not clear whether this was a transient or a more long-lasting depression of contractility. If the latter is the case, it might be possible that a depression of contractility could decrease shear forces on the aorta and therefore attenuate the development of atherosclerosis.

Accordingly, we have just completed a study in which we have treated animals with drugs that reduce contractility or blood pressure or both, and have measured the degree of atherosclerosis in these animals compared with a control atherosclerotic group.[18] Groups of animals were treated with metoprolol, 2.5 mg/kg/day, hydralazine, 2 mg/kg/day, and a combination of hydralazine plus metoprolol. Measurements of blood pressure showed variable effects, but there was a slight decrease in the group treated with metropolol plus hydralazine. When the animals were killed after 10 weeks on the high lipid diet, and the aortas examined, there was no significant difference between the percentage of aortic endothelial surface involved in any of the animal groups when compared with the atherosclerotic control animals. It does not appear, therefore, that any potential negative inotropic effect of verapamil is causally related to the drug's protective effect on the development of atherosclerosis. Overall, this is also suggested by the fact that nifedipine, a calcium-channel blocker with little negative inotropic effect when given in vivo, also exerts protective effects. Therefore, the data strongly suggest that the protective effects of calcium antagonists are related to a decrease in intracellular calcium.

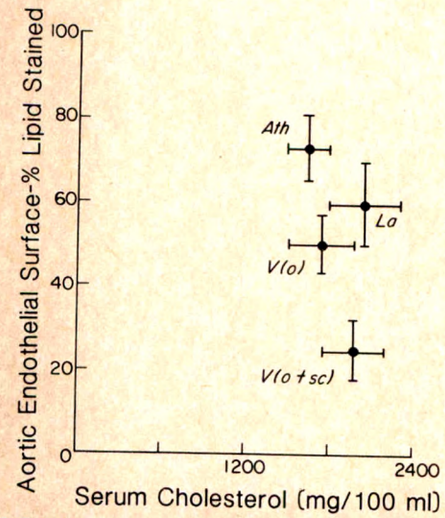

FIGURE 3. Relation of percentage of aortic surface area involved with atherosclerosis to mean serum cholesterol concentration during study. Rabbits treated with oral plus subcutaneous verapamil (V[o + sc]) had less surface area involved than did other groups ($p < 0.01$). Abbreviations as in Figure 1. Reproduced with permission from *JACC.*[16]

Most of the processes involved in atherogenesis require calcium-dependent energy from high energy phosphates. These include migration of arterial smooth muscle cells and macrophages into the intima, cell proliferation, connective tissue secretion and lipoprotein endocytosis. Calcium is also required for a number of other processes. These include the contraction-relaxation cycle in smooth muscle, directional cell movement as in chemotaxis, mitosis, adhesion of platelets to arterial connective tissue, platelet aggregation and the release phenomenon, as well as secretion of proteins, including collagen and also elastin, which binds lipoproteins to cell membrane receptors.

Elastin destruction and lesion calcification have also been suppressed by anticalcifying agents. Associated mechanisms requiring calcium include increased absorption of cholesterol by elastin due to calcium-induced changes in elastin configuration, complexing of lipoproteins to glycosaminoglycans, and calcium mineralization of connective tissue. Thus, in assessing the data from all studies cited in this review, the common theme appears to be that interventions capable of decreasing intracellular calcium exert a protective effect on the development of atherosclerosis.

Because a number of drugs given to patients can affect calcium, the potential clinical implications of these studies are evident. It should be pointed out, however, that the relevance of these animal models to human atherosclerosis is uncertain, and that there is a paucity of studies related to potential regression of atherosclerosis by interference with calcium flux. Specifically, there are no such studies available with the calcium-entry blockers. Additional studies will be necessary to determine whether or not the agents that interfere with calcium entry can also be effective in the regression process.

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Effects of Calcium-Channel Blocking Agents on Left Ventricular Diastolic Function in Hypertrophic Cardiomyopathy and in Coronary Artery Disease

ROBERT O. BONOW, MD

Abnormal left ventricular (LV) diastolic performance is a characteristic feature of hypertrophic cardiomyopathy (HC) and an important contributor to the development of symptoms. Impaired diastolic filling of the hypertrophied left ventricle results from both diminished distensibility and prolonged or incomplete relaxation. LV distensibility is not only influenced by fixed anatomic abnormalities (such as fibrosis or hypertrophy) that determine the passive elastic properties of the left ventricle, but also is modulated by the dynamics of myocardial relaxation: prolonged or incomplete LV relaxation may restrict the rate and extent of LV filling and result in altered pressure-volume relations throughout diastole. Several studies indicate that impaired LV relaxation and filling in HC may be modified favorably by verapamil or nifedipine administered on a short-term basis in the catheterization laboratory, associated with improved diastolic pressure-volume relations. Verapamil also improves LV filling during oral therapy. Improved indexes of LV filling correlate with symptomatic improvement, both short-term and long-term: Approximately 80% of patients having a persistent increase in peak LV filling rate have persistent improvement in objective exercise tolerance compared with preverapamil values.

Altered LV relaxation and filling are also often observed in patients with coronary artery disease (CAD) after myocardial infarction or during acute ischemia. Moreover, impaired filling occurs under resting conditions in many patients who have normal systolic function and no evidence of previous infarction. Nifedipine improves indexes of LV relaxation and distensibility during pacing-induced ischemia and verapamil improves indexes of LV filling at rest and during exercise-induced ischemia. In both HC and CAD, improved LV diastolic function by nifedipine or verapamil may reflect reduced ischemia, improved coronary flow, alterations in LV loading conditions or primary myocardial effects. These changes may contribute to the improvement in symptoms in many patients during treatment with these drugs.

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Diastolic function of the left ventricle in hypertrophic cardiomyopathy (HC) and coronary artery disease (CAD) has been the subject of intensive laboratory and clinical investigation. Altered left ventricular (LV) diastolic performance in these conditions results from impaired relaxation, diminished distensibility (or compliance) or both, and contributes importantly to the development and severity of symptoms. Several recent studies indicate that abnormal diastolic function in these conditions may be modified favorably by the calcium-channel blocking agents verapamil and nifedipine, which may relate, in part, to the improvement in symptoms in many patients during therapy with these drugs. Hence, it is pertinent to review the influence of LV diastolic dysfunction on the pathophysiologic features of the hypertrophied and ischemic left ventricle, and the evidence that the calcium-channel blocking drugs enhance LV relaxation and diastolic filling.

From the Cardiology Branch, the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland.

Address for reprints: Robert O. Bonow, MD, Building 10, Room 7B15, National Institutes of Health, Bethesda, Maryland 20205.

Hypertrophic Cardiomyopathy

Diminished LV diastolic filling in HC results in decreased cardiac output and increased LV filling pressures, thereby playing a pivotal role in the clinical manifestations of the disease. Two factors contribute to impaired diastolic filling of the hypertrophied left ventricle: decreased distensibility and impaired or incomplete relaxation. The dynamic influence of LV distensibility and LV relaxation on the magnitude and timing of LV diastolic filling may be examined in the context of the instantaneous relation between LV

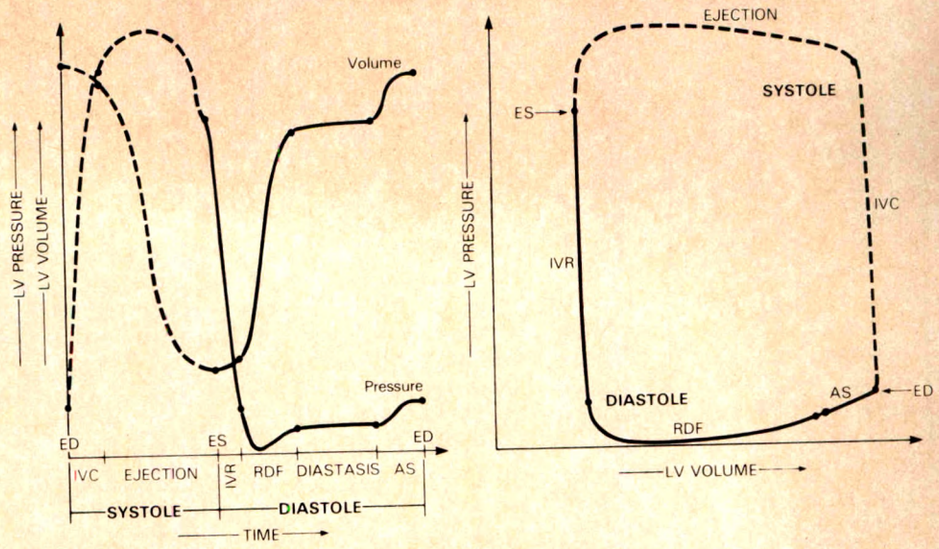

FIGURE 1. Left ventricular (LV) pressure-volume relations. **Left,** simultaneous pressure-time and volume-time curves during cardiac cycle. **Right,** instantaneous pressure-volume relation. AS = atrial systole; ED = end diastole; ES = end systole; IVC = isovolumic contraction; IVR = isovolumic relaxation; RDF = rapid diastolic filling.

pressure and LV volume throughout diastole (Fig. 1). Simultaneous LV pressure versus time and volume versus time curves during the cardiac cycle are presented in Figure 1, left, and the resultant LV pressure-volume loop, the instantaneous pressure-volume relation at each phase of the cardiac cycle,[1] is presented in Figure 1, right. LV distensibility is determined by the contour and slope of the pressure-volume relation[2,3] during the filling phases of diastole: rapid diastolic filling, diastasis and atrial systole.

LV distensibility: In HC, increased myocardial mass and altered myocardial muscle properties (stemming from fiber disarray and fibrosis) produce an increase in stiffness and a decrease in distensibility of the left ventricle,[2–5] manifested by a steeper slope of the LV pressure-volume relation during diastolic filling compared with normal. The consequence of reduced LV distensibility is an exaggerated increase in diastolic pressure during LV filling for a given increase in diastolic volume, often resulting in a diminished rate and extent of LV filling despite increased LV filling pressures.[6,7] Although LV distensibility in this regard is determined by fixed, anatomic abnormalities intrinsic to the hypertrophied left ventricle, distensibility may also be influenced dynamically by reversible alterations in LV relaxation.

LV relaxation: LV relaxation is impaired in HC[8–14] and is the second major determinant of decreased LV diastolic filling. After termination of the isovolumic phase of LV relaxation, when the mitral valve opens and the phase of rapid ventricular filling begins, the LV pressure continues to subside despite the abrupt increase in LV volume (Fig. 1, left). The decrease in pressure despite increasing volume, even in the normal ventricle, clearly indicates that active LV relaxation continues beyond the isovolumic phase and well into the filling phase, and that alterations in the extent, rate and timing of LV relaxation will have significant impact on the extent and rate of LV rapid diastolic filling.

Numerous studies indicate that LV relaxation in HC may be prolonged or incomplete,[8–14] manifested by a prolonged isovolumic relaxation period, a decreased rate of diastolic LV wall thinning and a reduced rate of LV pressure decrease, which in turn results in impaired LV diastolic filling[9–12,15,16] (Fig. 2). Decreased LV relaxation also produces an increase in myocardial tone during the filling phase, thereby altering LV diastolic pressure-volume relations.[2,5,17] Hence, LV distensibility is determined not only by fixed anatomic changes of the hypertrophied myocardium but also by potentially reversible alterations in LV filling dynamics[4] resulting from impaired relaxation.

LV relaxation is an active, energy-dependent process utilizing high-energy phosphates, directed at dissipation of muscle activation (inactivation) primarily by sequestering calcium ions in the sarcoplasmic reticulum; this lowers calcium ion concentrations in the cytosol in

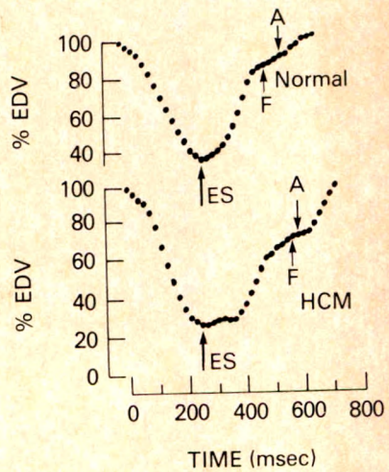

FIGURE 2. Left ventricular time-activity curves obtained by radionuclide angiography in a normal subject and a patient with hypertrophic cardiomyopathy (HCM), measuring relative volume changes throughout average cardiac cycle. Impaired diastolic function is evident in hypertrophic curve: prolonged isovolumic relaxation phase, decreased rate of rapid diastolic filling, decreased contribution of rapid filling to left ventricular filling volume and increased contribution of atrial systole. A = onset of atrial systole (measured electrocardiographically); ES = end-systole; F = termination of rapid filling.

the region of the myofibrillar contractile proteins[18] and produces actin-myosin dissociation. Laboratory and clinical studies indicate that the energy-dependent mechanisms responsible for this process are sensitive to low levels of ischemia[17–22] and to hypertrophy.[23–25] In addition to these inactivation-dependent mechanisms, LV relaxation is also influenced importantly by LV loading conditions,[26,27] including the rate and extent of coronary blood flow, regional LV nonuniformity or asynchrony, end-systolic pressure and end-systolic volume.[26–29] Any or all of these mechanisms may contribute to impaired relaxation in patients with HC.

Influence of calcium-channel blocking agents: Several studies have demonstrated that abnormal LV diastolic function in HC may be modified favorably by calcium-channel blocking agents. In the studies of Hanrath et al,[30] acute intravenous verapamil administration improved echocardiographic indexes of LV relaxation and filling, manifested by a decrease in the isovolumic relaxation period and an increase in the peak rate of LV posterior wall thinning. Using combined radionuclide and hemodynamic measurements, we have observed an improvement in LV relaxation and filling in a subset of patients with both obstructive and nonobstructive HC after acute intravenous verapamil;[31] the time constant of relaxation diminished and the peak rate of LV filling increased. In patients with such early diastolic changes, the LV diastolic pressure-volume curve was shifted downward and rightward, indicating an improvement in pressure-volume relations (Fig. 3). Indexes of LV diastolic function improved in these patients after acute verapamil administration despite evidence of a significant negative inotropic effect which, by itself, would be expected to cause further deterioration in LV diastolic performance. Similar improvement in LV diastolic pressure-volume relations after

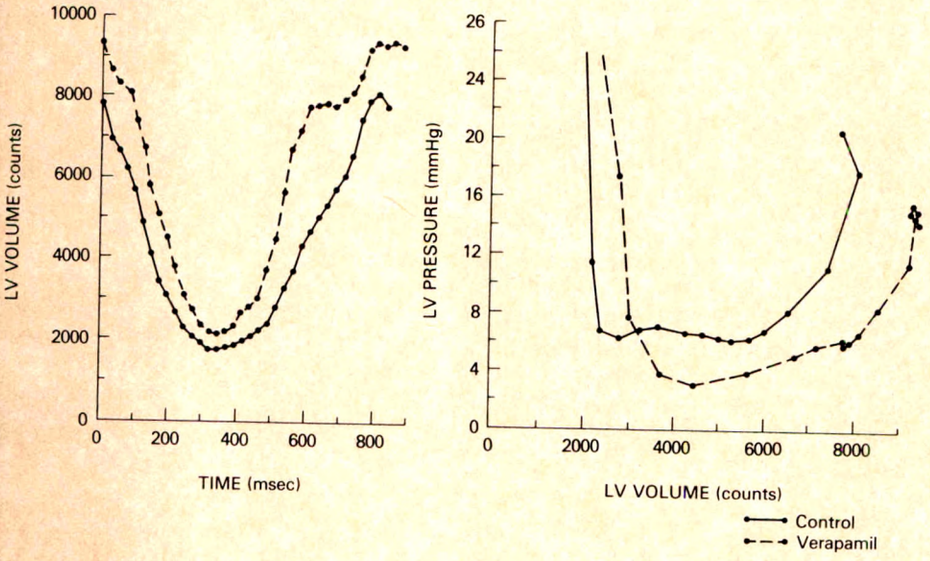

FIGURE 3. Effect of intravenous verapamil on left ventricular (LV) filling and diastolic pressure-volume relations obtained from combined radionuclide and hemodynamic measurements. In the volume curves (**left**), verapamil results in increased rate and extent of rapid filling, increase in stroke volume and reduced contribution of atrial systole. These changes are associated (**right**) with a downward and rightward shift in pressure-volume curve, indicating improved pressure-volume relations. Reprinted with permission from *Circulation*.[31]

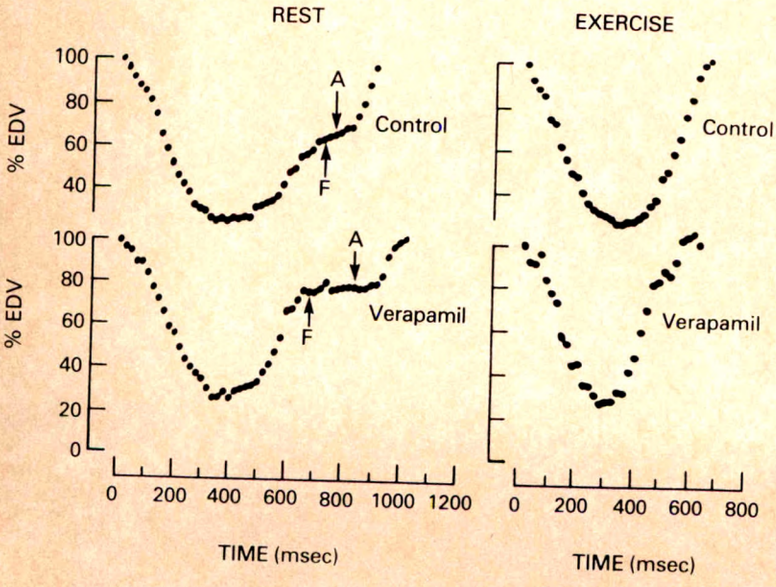

FIGURE 4. Left ventricular volume curves by radionuclide angiography at rest and during exercise in patient with hypertrophic cardiomyopathy. Oral verapamil (480 mg/day) results in enhanced diastolic filling at rest: shortened isovolumic phase, increased rate and extent of rapid diastolic filling and reduced contribution of atrial systole to total filling volume. Increased rate of filling is also evident during exercise. Each point represents 20 ms. EDV = end-diastolic volume.

erapamil administration have been reported by Chatterjee et al.[32] Improved LV relaxation, filling and diastolic pressure-volume relations have also been reported after the short-term administration of nifedipine in patients with nonobstructive HC by Lorell et al,[33] using combined hemodynamic-echocardiographic techniques, and by Senn et al,[34] using echocardiography.

Verapamil and nifedipine may improve indexes of LV relaxation and diastolic function in HC by direct effects on myocardial inactivation or by decreasing ischemia, increasing coronary blood flow or altering the loading conditions of the left ventricle. In this regard, Paulus et al[35] recently compared the relative effects of acute nitroprusside and nifedipine administration on LV relaxation, filling and distensibility in patients with nonobstructive HC. Despite similar decreases in systemic arterial pressure, nifedipine was associated with an increase in LV distensibility as well as less prolongation of LV isovolumic relaxation and less depression of peak LV filling rate compared with nitroprusside. These data suggest that nifedipine enhances LV diastolic performance independent of its vasodilatory properties.

Oral verapamil administration also improves LV diastolic filling, as assessed noninvasively by radionuclide angiography, during both short- and long-term therapy. With this technique, quantitative indexes of LV systolic and diastolic function are derived from analysis of LV time-activity curves, which represent relative changes in LV volume during the average cardiac cycle. In most patients with HC studied by this technique,[15,16] LV rapid diastolic filling is impaired, manifested by diminished peak filling rate, prolonged interval from end-systole to peak filling rate, reduced contribution of rapid diastolic filling to total LV stroke volume and increased contribution of atrial systole (Fig. 2). After 1 to 2 weeks of oral therapy (320 to 640 mg/day), verapamil does not affect indexes of LV contractile function but significantly alters indexes of diastolic filling at rest (Fig. 4): increased rate and extent of rapid diastolic filling, shortening of the period from end-systole to peak filling rate and reduced contribution of atrial systole to LV filling volume.[15,16] After 1 to 2 years of oral therapy, the improvement in LV diastolic filling is less marked than the initial short-term improvements.[36] However, when verapamil is withdrawn after 1 to 2 years, LV diastolic filling deteriorates, indicating a persistent reversible effect of the drug on LV diastolic function. In contrast, β blockers do not appear to affect LV diastolic performance in HC.[15,37]

Radionuclide angiographic studies performed during exercise[38] also demonstrate enhanced LV diastolic filling after verapamil (Fig. 4); similar improvement in diastolic indexes of LV function have been observed during exercise during oral nifedipine therapy.[38] These findings are consistent with the hemodynamic data from a study by Hanrath et al,[39] in which a decrease in LV filling pressures during exercise was measured after 7 weeks of oral verapamil administration. Hence, enhanced LV diastolic performance may account, at least in part, for the objective improvement in exercise tolerance frequently seen in patients during verapamil therapy.[40,41] In this regard, improved indexes of LV diastolic filling, measured at rest, correlate significantly with improvement in symptoms, both short-term (1 week to 1 month) and long-term (1 to 2 years).[42] During long-term studies, 80% of patients with a persistent increase in peak LV filling rate have persistent improvement in exercise tolerance relative to preverapamil values, compared with only 11% of patients in whom peak filling rate remains unchanged or decreased relative to preverapamil values. These data suggest that enhanced LV relaxation and filling are important mechanisms by which many patients with HC experience improvement in symptoms during treatment with verapamil.

Coronary Artery Disease

LV relaxation and distensibility: Abnormal LV diastolic performance is a common manifestation of CAD. As in HC, LV diastolic dysfunction in CAD arises from impaired LV relaxation, reduced LV distensibility or both. In patients with previous myocardial infarction, with or without diminished LV regional and global systolic function, diastolic dysfunction results primarily from myocardial fibrosis, with alterations in the distensibility characteristics of the left ventricle.[2,3,43–46] During periods of active ischemia, myocardial inactivation is inhibited, and LV relaxation is prolonged or incomplete, thereby altering LV filling characteristics and aggravating diastolic pressure-volume relations.[17,19,47–52] Hence, reversible decreases in LV distensibility may occur on the basis of impaired LV relaxation stemming from transient LV ischemia (Fig. 5). Impaired LV diastolic function may also occur under resting conditions in many patients with CAD in whom LV contractile function is normal and in whom there is no evidence of either previous myocardial infarction or active myocardial ischemia.[53–56] In many such patients, impaired LV filling under resting conditions improves after successful percutaneous transluminal coronary

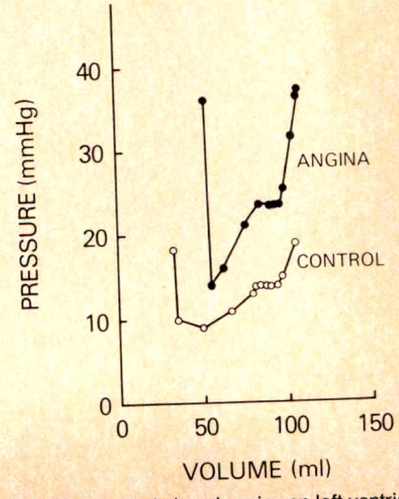

FIGURE 5. Effect of pacing-induced angina on left ventricular diastolic pressure-volume relation in coronary artery disease. Reprinted with permission from *Eur J Cardiol.*[52]

angioplasty,[57] with no concomitant change in resting heart rate or ejection fraction, suggesting that these diastolic abnormalities in CAD are not fixed but may be modified by the extent of reversible myocardial ischemia or reduced coronary flow. Moreover, recent data suggest that impaired diastolic filling in patients with normal systolic function is associated with asynchronous LV regional function, and that improved diastolic filling after percutaneous transluminal coronary angioplasty is associated with a reduction in regional asynchrony.[58]

Influence of calcium-channel blocking agents: Impaired LV filling in patients with CAD also improves after short-term oral verapamil therapy,[59] both at rest and during exercise-induced ischemia (Fig. 6). Similarly, Lorell et al[60] demonstrated improvement in LV relaxation and distensibility during pacing-induced ischemia in patients with CAD treated acutely with sublingual nifedipine. Enhanced LV diastolic function after administration of verapamil or nifedipine may, as with percutaneous transluminal coronary angioplasty, reflect alterations in the severity of reversible ischemia or the magnitude of coronary flow. Alternatively, these agents may have direct effects on myocardial metabolism and inactivation. In this regard, the data of Nayler and Williams[18] suggest that disturbances of intracellular calcium metabolism during myocardial ischemia may account, at least in part, for incomplete or impaired relaxation and altered diastolic tone. Impaired myocardial relaxation during hypoxia appears to be reversible under some experimental conditions and may be modified by intracellular calcium availability.[20,61] Lorell and Barry[62] demonstrated impaired relaxation in cultured chick embryo ventricular cells exposed to a high concentration of external calcium; this inhibition of relaxation was reversed by verapamil. Hence, impaired LV relaxation resulting from reduced myocardial inactivation during acute ischemia may possibly be improved by verapamil, nifedipine and other agents that reduce calcium ion flux across the myocardial membrane.

Enhanced diastolic performance of the intact left ventricle by calcium-channel blocking drugs may also arise from changes in LV loading conditions, such as blood pressure, heart rate and LV contractile function. Although it is impossible to separate completely the potential influence of altered LV loading conditions on verapamil- or nifedipine-induced improvement in LV relaxation and filling in the intact heart, recent data of Urquhart et al[63] suggest that verapamil may exert beneficial effects on LV diastolic function independently of changes in LV loading conditions. In these hemodynamic studies, dose-response curves to verapamil in dogs during acute ischemia indicated that the rate of LV diastolic filling increased before measurable changes in heart rate, left atrial pressure or systemic blood pressure were observed.

Although LV relaxation and filling in CAD are depressed by myocardial ischemia, these altered diastolic properties of the left ventricle may also potentiate ischemia and contribute to symptom production. For example, reduced LV relaxation with associated impairment in the rate and extent of LV diastolic filling and reduced LV distensibility may result in increase in LV filling pressures (Fig. 5) and symptoms of dyspnea frequently observed in patients with CAD during acute myocardial infarction or reversible ischemia. Moreover, reduction in the rate of decrease of early diastolic ventricular wall tension resulting from prolonged or in-

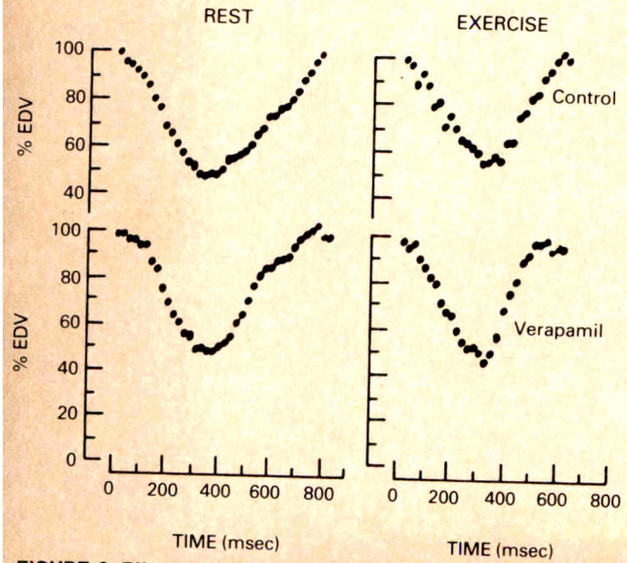

FIGURE 6. Effect of oral verapamil (480 mg/day) on left ventricular diastolic filling in patient with coronary artery disease. Radionuclide angiographic volume curves demonstrate increased rate of diastolic filling both at rest and during exercise. Each point represents 20 ms. EDV = end-diastolic volume.

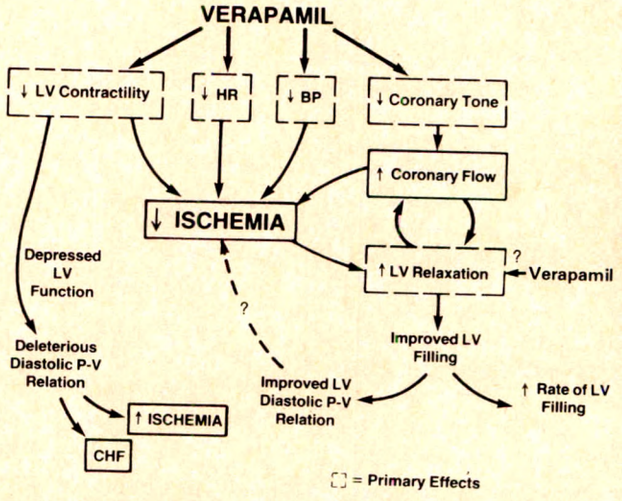

FIGURE 7. Mechanisms of verapamil effects in coronary artery disease. Primary actions include both a decrease in myocardial oxygen requirements (through decreases in left ventricular [LV] contractility, heart rate [HR], and blood pressure [BP]) and increase in coronary blood flow (through coronary artery dilatation and, possibly, enhanced left ventricular relaxation). Improved relaxation may also be a manifestation of decreased ischemia or altered loading conditions. Significant negative inotropic effects in isolated patients may lead to deleterious diastolic pressure-volume (P-V) relations, which may aggravate angina or precipitate symptoms of pulmonary congestion. Similar mechanisms apply to nifedipine, with exception of minimal primary effects on contractility and heart rate.

complete relaxation may impede regional anterograde and collateral coronary flow, and alterations in LV distensibility, with increased LV diastolic pressures, may aggravate end-diastolic wall stress and increase myocardial oxygen requirements. If these mechanisms are operative, LV diastolic dysfunction in CAD, as in HC, may contribute to the severity of symptoms; amelioration of these diastolic abnormalities by calcium-channel blockers may contribute to the improvement in symptoms in many patients during treatment with these agents. For these reasons, it is helpful to consider enhanced LV relaxation as a potential primary effect in the complex and interrelated mechanisms of action of the calcium-channel blockers in CAD (Fig. 7).

In conclusion, decreased LV distensibility and impaired LV relaxation are characteristic features of HC that result in impaired LV diastolic filling. These factors undoubtedly contribute to the pathophysiologic mechanisms leading to the development of symptoms in these patients. Impaired LV relaxation may play an analogous role in patients with CAD. Both verapamil and nifedipine favorably modify indexes of LV diastolic performance by way of a decrease in ischemia, salutary alteration in LV loading conditions or direct effects on myocardial inactivation. These actions suggest that enhanced LV diastolic function is an important primary or secondary mechanism contributing to the beneficial effects of these drugs in the hypertrophied or ischemic left ventricle.

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Microvascular Spasm as a Cause of Cardiomyopathies and the Calcium-Blocking Agent Verapamil as Potential Primary Therapy

EDMUND H. SONNENBLICK, MD, FREDERICK FEIN, MD, JOSEPH M. CAPASSO, PhD, and STEPHEN M. FACTOR, MD

The origin of cardiomyopathies, a major cause of cardiac disability and death, has been largely unexplained. Pathologic features, common to all cardiomyopathies independent of origin, include ventricular hypertrophy and diffuse scarring with variable amounts of ventricular dilatation. This problem was studied experimentally in 2 models of congestive cardiomyopathy: the hereditary cardiomyopathic Syrian hamster and the hypertensive-diabetic rat. In both the genetic and the acquired disease models, there is focal myocytolytic necrosis followed by healing with focal scars, ventricular wall hypertrophy, ventricular dilatation with congestive heart failure and, ultimately, death. In view of the heterogeneous pathologic features of both diseases, silicone rubber perfusions have been used to study the microcirculation of the heart in these animals; microvascular spasm has been demonstrated early in the disease associated with small areas of myocytolytic necrosis that undergo subsequent fibrosis. Reactive hypertrophy then ensues as a compensatory response to this myocellular necrosis; it is the combination of cell loss and slowly decreasing contractility resulting from the reactive hypertrophy, which culminates in a cardiomyopathy. Administration of verapamil or prazosin to the cardiomyopathic Syrian hamster prevents microvascular spasm and development of cardiomyopathic changes in the myocardium. In view of these and other findings related to the anatomy and hyperreactivity of microcirculation, it is concluded that hypertrophic congestive cardiomyopathies may be caused by focal cell loss due to microvascular spasm and reperfusion injury, with the subsequent development of focal fibrosis and reactive hypertrophy in response to the myocardial necrosis. Myocytes in the cardiomyopathic heart may also be abnormal so that they are unable to tolerate transient focal ischemia without becoming necrotic. A suggestion is made that the ultimate therapy of cardiomyopathies may involve the early treatment of the microvascular spastic lesion in order to prevent further myocardial cell loss. Support of myocardial contractility and treatment of peripheral circulatory defects late in the process of this disease can then only be viewed as largely palliative.

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The study and treatment of dilated, congestive cardiomyopathies has focused predominantly on the late stages of disease when clinical symptoms are already evident. Although the treatment of congestive heart failure has improved with the development of new inotropic agents and application of peripheral vasodilator therapy, these approaches are essentially palliative in that they do not appear to alter the underlying pathologic cause of failure, nor do they change the fatal outcome of the process. Thus, the pathogenesis of primary myocardial failure, which results in ventricular dysfunction, depressed cardiac pump performance and, ultimately, in clinically apparent congestive heart failure, remains unsolved. The fact that short- or long-term patient survival appears to be intimately associated with the extent of myocardial dysfunction regardless of its origin,[1] emphasizes the importance of preserving myocardial function if mortality rate is to be altered. In this report we review some recent data from our laboratories concerning the cause of myocardial failure in several different models of cardiomyopathy,

From the Departments of Medicine (Division of Cardiology) and Pathology, Albert Einstein College of Medicine, New York, New York. This study was supported in part by Grants HL-18824, HL-20426 and HL-23171 from the National Heart, Lung, and Blood Institutes, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Edmund H. Sonnenblick, MD, Department of Medicine (Division of Cardiology), Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461.

which may be directly relevant to the treatment of the disease in man.

Components of Heart Failure

There are 2 components to the syndrome of heart failure. The first is myocardial failure, which is characterized by a decrease in the capacity of heart muscle to develop force and shorten normally with ultimate depression of pump function. Such myocardial failure is frequently associated with pressure overloads and resultant hypertrophy, or with either segmental or diffuse loss of myocardium, which is subsequently associated with variable amounts of reactive hypertrophy in response to the cell loss. Ventricular dilatation occurs as pump function decreases. In the congestive cardiomyopathies, ventricular failure is generally considered to result from diffuse myocellular dysfunction of unknown origin.

The second component is congestive heart failure, which is the systemic response to inadequate pump function, characterized by an inability to augment cardiac output to meet peripheral organ requirements. Sympathetic nervous system activity and renal vasoconstriction occur with activation of the renin-angiotensin system, leading to augmented peripheral vascular resistance, peripheral congestion and edema. The treatment modalities available in this syndrome are largely directed toward these peripheral factors. However, treatment that begins after pump failure does little to alter the significantly damaged myocardium except when a substantial pressure or volume overload can be removed. The question arises, however, if anything can be done to affect and arrest the process of myocardial failure before it becomes severe. In order to develop a rational approach for the treatment of cardiomyopathies, the mechanisms by which myocardial failure occurs in the absence of abnormal loading require definition.

The role of hypertrophy per se in producing myocardial failure remains at issue. Although hypertrophy resulting from renovascular hypertension leads to a slowing of myocardial contraction and relaxation,[2] these contractile changes are totally reversible within broad limits when the overload is removed. Thus, myocardial hypertrophy alone is not an adequate explanation for irreversible myocardial failure. Segmental myocardial necrosis associated with obstructive coronary vascular disease may also result in acute ventricular failure if sufficient muscle mass is lost;[3] this loss of myocardium creates an excess load for the noninfarcted portion of the heart, which leads to the development of compensatory or reactive hypertrophy.[4] In attempts to normalize the load for a fixed number of nonproliferating myocytes, the myocardial cell can only increase in mass, not number. If compensation is adequate, the heart may function normally for a considerable period of time. However, either progressive cell loss secondary to supervening ischemic events or the hypertrophic process itself, which can lead to myocellular contractile dysfunction,[5,6] may eventuate in myocardial failure even when further ischemia is absent. These alterations may then create a late-stage picture in ischemic heart disease of congestive myopathy. The process of segmental myocardial loss in acute myocardial infarction with subsequent compensatory hypertrophy as described earlier is relevant to the problem of "idiopathic," dilated, congestive cardiomyopathy. Although idiopathic cardiomyopathies have been considered the result of a diffuse process that affects the myocardial cells equally throughout the ventricle, the pathologic features are rather focal and nonspecific.[7–9] Typical findings in human congestive cardiomyopathy include a large heart, either firm or flabby, with prominent ventricular dilatation, and interstitial fibrosis with focal, discrete zones of myocytolytic necrosis leading to replacement scarring associated with variable degrees of myocellular hypertrophy of uninvolved muscle. None of these pathologic features is characteristic solely of cardiomyopathy. Similar alterations may also be seen in the hearts of patients with significant obstructive coronary artery disease.

Our interest in the pathologic features of cardiomyopathy was stimulated by the focal nature of the processes in the ventricular wall. Despite the generally accepted view that cardiomyopathies result from diffuse myocellular disease, the absence of diffuse pathologic abnormalities, at least in the early stages, suggests that there may be focal events affecting discrete, small volumes of tissue accounting for the myocardial degeneration. Studies of several experimental models have enabled us to pinpoint these focal events.

Experimental Studies of Cardiomyopathies

We have studied 2 distinct models of cardiomyopathy in animals that are characterized by degenerative myocardial lesions similar to those observed in human cardiomyopathies. The hearts of Syrian hamsters[10–12] with hereditary cardiomyopathy and rats with combined hypertension and diabetes[13–15] have shown regions of focal fibrosis and myocytolysis associated with hypertrophied but otherwise normal-appearing muscle.

The Syrian hamster provides a unique genetic model of a cardiomyopathy. Focal myocardial necrosis begins as early as 1 month of age, leading to congestive heart failure within a year. The pathogenesis of the myocytolytic necrosis characteristic of the problem is unknown, but it has been suggested that there is increased calcium flux across the sarcolemma, leading to cellular hypercontraction, mitochondrial calcification and cell death.[16,17] These observations would suggest that there is a diffuse and probably uniform cellular abnormality. Why then should the pathologic features be focal in nature? Although the possibility that these focal necrotizing lesions are mediated by abnormalities of the microcirculation has been considered, no significant changes have been observed in these vessels when routine histologic methods were used.

To evaluate the role of the microvasculature in the cardiomyopathy of the Syrian hamster, a series of perfusions with silicone rubber solutions were performed in living animals.[12] This material perfuses the entire microcirculation; after tissue clearing, the microvasculature can be visualized in intact myocardium in a 3-dimensional array. Studies of such cleared specimens in cardiomyopathic hamsters at different stages of the

disease reveal frequent areas of microvascular constriction, diffuse narrowing and luminal irregularity (Fig. 1), strikingly similar to vascular spasm observed in larger vessels during angiography.[12] Areas of severe focal constriction in small arterioles were often seen proximal to the necrotic and scarred myocardium rather than within these areas per se in the late stages of disease (90 to 150 days). In earlier stages (30 to 50 days), before development of extensive necrosis, the spastic changes were also observed, suggesting that spasm was a cause rather than an effect of the necrotizing process. Routine sectioning of nonperfused hearts failed to reveal fixed structural lesions in the small myocardial vessels, and direct histologic visualization of vessels with marked hyperreactivity demonstrated that the luminal narrowing was not the consequence of anatomic lesions in the microcirculation. Thus, although structural lesions in these vessels could produce the same appearance with silicone rubber microangiography, the absence of vessel wall pathologic features supports the view that these lesions represent a dynamic process consistent with microvascular spasm.

Further evidence that microvascular hyperreactivity contributes significantly to myocardial degeneration in the cardiomyopathy of the Syrian hamster comes from studies with the "slow-channel" calcium-blocking agent and coronary vasodilator verapamil. Significantly, pretreatment of young hamsters with 0.5 mg of verapamil twice a day (bid) subcutaneously before development of focal myocardial necrosis (30 to 50 days) abolishes the microvascular spasm[12] and prevents myocytolytic lesions. Recent studies showing prevention of vascular lesions using the α-adrenergic blocking agent prazosin (6 to 8 mg/kg bid subcutaneously) provide further evidence that the microvasculature in the hamster heart undergoes spasm leading to focal myocardial necrosis.[18] Prazosin markedly diminished the frequency of spasm in precapillary arterioles, and there was a highly significant decrease in myocardial necrosis in the treated versus the untreated cardiomyopathic animals (0.66 versus 8.80% of ventricular area necrotic, respectively). The promising results with verapamil and prazosin must still be viewed with caution, because, to date, we have prevented microvascular spasm and myocytolytic necrosis only during the early stages of active necrosis (30 to 50 days), and have yet to treat animals in the hypertrophic (150 to 250 days) or the congestive (250 to 350 days) stages with these drugs.

Based on these preliminary results, however, we have tentatively concluded that in the cardiomyopathic hamster, focal, transient spasm of small blood vessels causes myocytolytic necrosis leading to scar formation and reactive hypertrophy, which eventuates in the cardiomyopathy. This does not exclude the possibility that the myocytes may also be abnormal,[16,17] which may make them susceptible to infarction during the ischemia induced by the episodic microvascular spasm. Indeed it is possible that a defect in cell surface function that fails to exclude calcium from the cell may produce both vascular spasm and a tendency for reperfusion type myocardial cell necrosis in the areas subserved by the spastic small vessels.

Studies of the hypertensive diabetic rat,[13] an experimental model of an acquired disease initially described in humans,[19] reveal morphologic features similar to other forms of cardiomyopathy. When diabetes is induced in rats by streptozotocin, abnormalities of myocardial contraction occur characterized by slowing of contraction and delayed relaxation.[20] It is noteworthy that no histologic alterations occur, and all of the functional abnormalities are reversed by the administration of insulin.[21] Similarly, when renal hypertension is produced in rats, ventricular hypertrophy occurs with contractile abnormalities similar to those described in the diabetic rat. Again, these changes are all reversible when the hypertension is reversed and the hypertrophy resolves.[22]

However, when experimental 1-clip, 2-kidney renovascular hypertension is superimposed on streptozotocin-induced diabetes, major pathologic changes occur

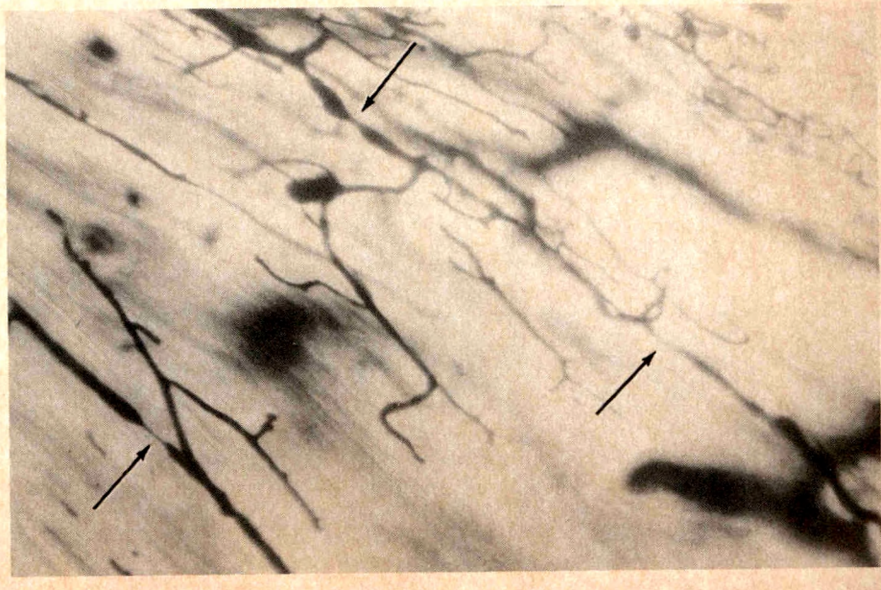

FIGURE 1. Silicone rubber-perfused region of cleared myocardium from 44-day-old cardiomyopathic Syrian hamster. Note numerous focal constrictions (**arrows**) in arteriolar-sized vessels in this field, which are consistent with microvascular spasm. Although fixed structural lesions in these vessels could produce same appearance, no such lesions were demonstrated in routine sections. Furthermore, pretreatment of these animals with verapamil abolished spasm and prevented development of myocardial necrosis (magnification ×155).

with myocytolytic necrosis, replacement fibrosis and myocellular hypertrophy, similar to those seen in the cardiomyopathic hamster. In this model, streptozotocin was injected 1 week after left renal artery stenosis was produced in young female Wistar rats. In addition to the replacement fibrosis typical of hamster cardiomyopathy, there is also extensive interstitial deposition of collagen and basement membrane material around blood vessels and hypertrophied myocardial cells. Studies of the microcirculation in this model with in vivo silicone rubber perfusions have revealed numerous microvascular constrictions, tortuosities and microaneurysms.[14,15] Semiquantitative analysis of these microvascular abnormalities in hypertensive-diabetic animals after 8 weeks of combined hypertension and diabetes revealed a highly significant increase of lesions when compared with normal control subjects and normotensive diabetic animals.[15] Nondiabetic hypertensive animals had an intermediate number of vascular lesions, consistent with the intermediate degree of myocardial degeneration we have shown previously.[13] The vascular abnormalities, which are similar to those we described in the cardiomyopathic hamster heart, may account for the extensive myocytolytic myocardial necrosis. The interstitial scarring, however, may be secondary to increased microvascular permeability related to both the diabetic state and the hypertension. The combination of these 2 vascular insults may lead to accelerated leakage of fluid into the interstitial space. Williamson and Kilo[23] proposed that extravascular plasma constituents might stimulate synthesis of basement membrane material and collagen in diabetes, leading to such fibrosis. In addition, studies of ventricular papillary muscles isolated from animals that were both hypertensive and diabetic for 4 to 5 months revealed profound electrophysiologic and mechanical changes, which were more severe than in animals with isolated diabetes or hypertension.[24,25] A high mortality rate (55%) was observed over a 7-month period of observation and postmortem studies revealed a high frequency of acute and chronic pulmonary and hepatic congestion.[26]

Overall, the focal nature of the lesions in this disease strongly suggests that the microcirculation mediates myocellular necrosis and interstitial collagen deposition. Both processes could cause myocardial dysfunction by limiting the number of myocardial units available for contraction, by stimulating the development of hypertrophied muscle in unaffected zones and by stiffening the ventricle through interstitial scarring, which may lead to diminished diastolic compliance.

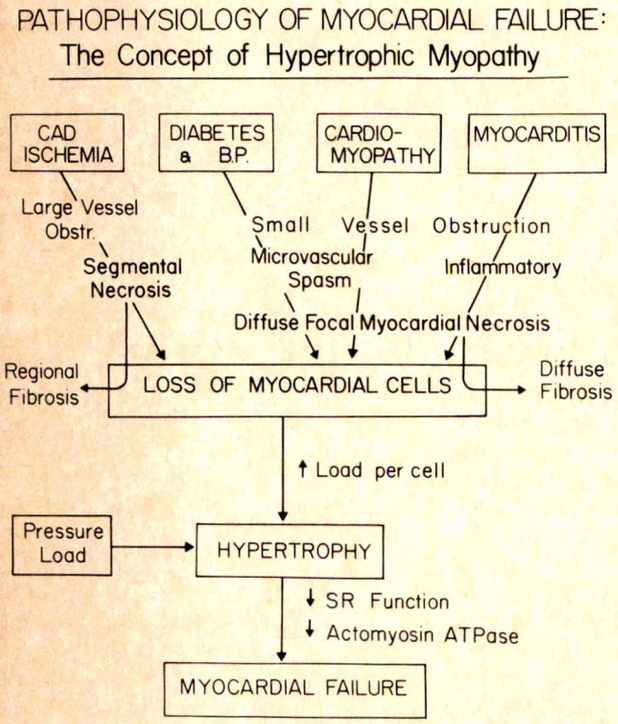

FIGURE 2. Our conceptual view of myocardial failure. Many different processes, including ischemic coronary artery disease (CAD), diabetes mellitus and hypertension (BP), some forms of cardiomyopathy including that seen in the hamster and myocarditis, may lead to loss of myocardial cells. This cell loss can develop from large-vessel obstruction producing segmental necrosis, as in acute myocardial infarction, microvascular spasm causing focal necrosis and inflammatory processes of unknown nature that may affect microcirculation or myocardial cells directly. Resultant loss of myocytes increases the load per cell, stimulating hypertrophy of unaffected myocardium. End-stage of myocardial failure results from inadequate numbers of cells to pump effectively, stiffening of myocardium due to connective tissue deposition and decreased function associated with pathologic cellular hypertrophy. Although myocardial failure may occur rapidly with myocardial infarction, in cardiomyopathy these processes may take years to develop and they may not be clinically apparent until patient presents with congestive heart failure. ATPase = adenosine triphosphatase; SR = sarcoplasmic reticulum.

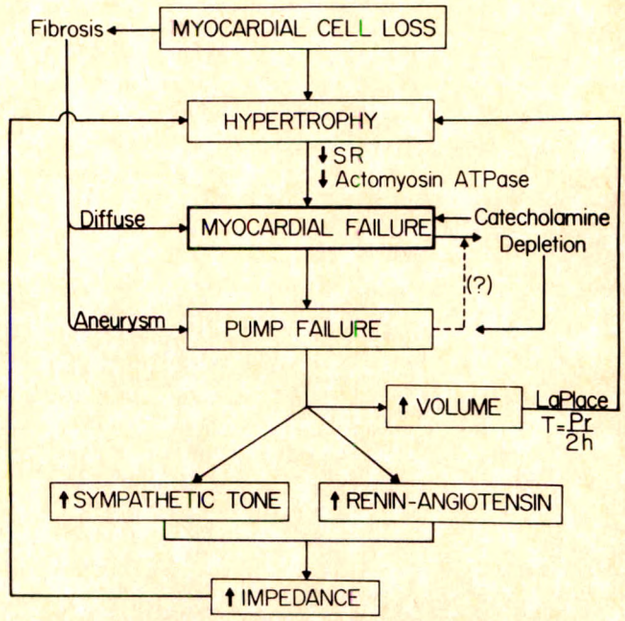

FIGURE 3. Interrelations between myocardial cell loss and pump failure. Myocardial cell loss leads to both reactive hypertrophy and myocardial failure. Ultimately, pump failure ensues, which initiates compensatory responses that feed back to create secondary overloads and more hypertrophy and failure. This secondary impedance increase as well as volume overload may extend initial pump dysfunction. ATPase = adenosine triphosphatase; H = radius; P = pressure; SR = sarcoplasmic reticulum; T = tension.

Our studies of the Syrian hamster and the hypertensive-diabetic rat with cardiomyopathies suggest that microvascular spasm plays a significant role in the development of myocardial degeneration and failure. However, a crucial question remains: can transient obstruction of the microcirculation cause small areas of discrete myocardial necrosis? A hypothetic requirement for this process to occur is for the microcirculation to be organized into an end-vessel system. If capillaries were diffusely interconnected by anastomoses, then localized microvascular obstruction would not be likely to produce necrosis of small volumes of tissue. Recent studies in our laboratory have, in fact, shown that the cardiac microcirculation is arranged into end-capillary loops without intercapillary connections in the dog[27] and human,[28] and we have reason to believe that a similar pattern exists in rodents (unpublished observations, 1981). We also have demonstrated that embolization of 25 or 50 μm microspheres into the coronary microcirculation of dogs and rats leads to focal myocytolytic necrosis very similar to what we described in the cardiomyopathic hamster and the hypertensive-diabetic rat.[29] Variation in the size of necrotic lesions may depend on the size of the vessel occluded, because 50 μm microspheres produced larger lesions than 25 μm beads. Variably sized necrotic lesions in clinical and experimental diseases may be explained by similar mechanisms. An interesting observation from our experimental models of cardiomyopathy is that necrosis developing secondary to microembolization appears to be due to vasospasm. Pretreatment of animals with phentolamine (an α-adrenergic blocking agent) before embolization prevented necrosis in the dog, suggesting that anatomic obstruction of the microvasculature by beads alone was not the cause of tissue necrosis.[29]

In summary, our recent investigations reveal that microvascular spasm is present in the cardiomyopathic Syrian hamster, the hypertensive-diabetic rat and the myocardial microcirculation of the dog and rat embolized with microspheres. In the models of congestive cardiomyopathy, it appears that microvascular spasm leads to focal cell necrosis and subsequent myocardial scarring. From these varied observations we have speculated that such microcirculatory events are a general feature of congestive cardiomyopathy. If so, microvascular lesions may explain not only the pathologic features of cardiomyopathy, but also the occasional presence of atypical angina-like chest pain in patients in whom the large coronary arteries are normal.

It appears then that there are many common features in congestive cardiomyopathy as well as in ischemic congestive heart failure associated with obstructed coronary arteries. These similarities are summarized in Figure 2. Microvascular spasm in cardiomyopathy producing focal myocardial necrosis, obstructive coronary artery disease causing segmental myocardial necrosis and, possibly, inflammatory myocarditis leading to loss of myocardial cells will all eventuate in a decreased number of nonproliferating myocytes. This cell loss increases the load borne by the remaining unaffected myocytes, leading to their compensatory hypertrophy. Subsequently, with extensive focal scarring and interstitial fibrosis, a threshold number of cells may be lost and compensation is no longer adequate. In addition, both replacement and interstitial fibrosis may limit overall ventricular compliance. Ventricular dilatation may supervene in an attempt to compensate for decreased myocardial function. Thus, what began as widespread focal and even clinically silent necrosis possibly secondary to microvascular spasm may terminate as a typical dilated and hypertrophied heart, ultimately causing congestive heart failure (Fig. 2 and 3).

One may speculate that microvascular spasm producing transient focal ischemia may result in reversible chest pain without persistent damage in the otherwise normal heart. When myocytes are abnormal with decreased ability to handle calcium loads,[17] similar transient focal ischemia may eventuate in a cardiomyopathy. Recent evidence of sarcolemmal defects in the Syrian hamster[30] raise the possibility that membrane abnormalities make the myocytes particularly susceptible to intermittent ischemia. In the hypertensive-diabetic rat, there may also be membrane alterations secondary to the diabetes, which, with the microvascular spasm associated with hypertension, may lead to accelerated focal myocardial abnormalities, with microvascular spasm mediating necrosis of cells that are unable to withstand transient ischemia.

If this concept of microvascular hyperreactivity is proven correct, it will provide an explanation for the heterogeneous pathologic features of congestive cardiomyopathy, and the paucity of alterations in the unaffected hypertrophied myocardial cells. Moreover, this hypothesis raises the possibility that understanding the pathogenesis of cardiomyopathy will allow specific drug therapy to be designed to prevent the progression of the disease process, even if the underlying myocellular defects cannot be treated. To date, therapy for congestive cardiomyopathy has been palliative and has used digitalis glycosides, catecholamines, vasodilators and diuretics, which in combination can increase myocardial contractility to improve ventricular performance and relieve pulmonary and systemic congestion. However, these agents do not halt the progression of the disease, and, in the case of inotropic agents, might actually increase the loss of myocardial cells secondary to microvascular spasm by enhancing calcium overloading of cells. Thus, it is not surprising that such therapy can improve symptoms without altering the fatal outcome of the disease process. In contrast, verapamil completely prevents myocardial necrosis and fibrosis and possibly the ultimate development of ventricular failure in the Syrian hamster. We hope that, in the future, treatment modalities that may affect the long-term prognosis will be designed for patients in the early stages of congestive cardiomyopathy. The findings presented here suggest that such a controlled therapeutic trial is currently warranted in man with enhanced survival being the clear and definitive endpoint to efficacy.

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Use of Calcium-Channel Blocking Drugs in Hypertrophic Cardiomyopathy

DOUGLAS R. ROSING, MD, ULLA IDÄNPÄÄN-HEIKKILÄ, MD, BARRY J. MARON, MD, ROBERT O. BONOW, MD, and STEPHEN E. EPSTEIN, MD

Verapamil exerts a wide spectrum of hemodynamic effects in patients with hypertrophic cardiomyopathy (HC), and its administration offers an important alternative to β-receptor blocker therapy in such patients. The intravenous administration of verapamil to 62 patients in the catheterization laboratory decreased systolic blood pressure from 118 ± 17 to 102 ± 17 mm Hg ($p < 0.001$). It had no significant effect on heart rate, mean pulmonary artery wedge pressure, left ventricular (LV) end-diastolic pressure or cardiac output; however, LV outflow gradient in the basal state decreased from 62 ± 34 to 29 ± 34 mm Hg ($p < 0.05$). These findings demonstrate a decrease in LV outflow tract obstruction. Radionuclide angiography indicated the major action responsible for the reduction in obstruction appears to be an improvement in LV diastolic function. Short-term nifedipine administration to patients with HC produced no significant effect on LV outflow tract gradients and early diastolic filling. Short-term double-blind studies showed that verapamil improved exercise time by 26 ± 35% ($p < 0.005$) compared with placebo, whereas propranolol improved it by 21 ± 35% ($p < 0.025$). In a separate study, verapamil improved exercise duration by 38 ± 58% ($p = 0.02$) compared with placebo, whereas nifedipine improved it by 20 ± 47% (difference is not significant). Verapamil resulted in a more beneficial subjective symptomatic response than propranolol or nifedipine when compared with placebo. Long-term verapamil therapy was instituted in 227 patients; 133 of these patients have continued taking the medication for an average of 25 ± 13 months because their quality of life improved compared with what they experienced with their former therapy (usually β blocker). Improved exercise capacity of 40% has been maintained in 32 patients for 2 years. A decrease in ventricular septal thickness of 1.5 ± 2.6 mm was also found in 32 patients studied after 39 ± 8 months of verapamil therapy. Nine patients died during follow-up study, but it is unclear whether the drug increased survival or, conversely, whether any of the deaths could be attributed to verapamil administration. Significant adverse electrophysiologic and hemodynamic effects were seen in 59 instances. The electrophysiologic events, atrioventricular block and sinus arrest, were definitely verapamil-related, but it is uncertain how many of the hemodynamic problems of hypotension and pulmonary congestion were drug-related. It was necessary to discontinue verapamil in only 7% of patients because of adverse effects. These studies indicate that verapamil offers an important alternative to β-blocker therapy in selected patients with HC.

(Am J Cardiol 1985;55:185B–195B)

Until recently, the primary pharmacologic therapy for treating patients with hypertrophic cardiomyopathy (HC) was the administration of β-adrenergic receptor blocking agents.[1–3] Although β-blocker therapy is often effective in improving symptoms, not all patients benefit by the use of this group of drugs and many patients have undesirable adverse effects from these agents. Operative intervention, usually ventricular septal myectomy,[4] but occasionally mitral valve replacement,[5] offers an additional therapeutic approach. However, patients without significant left ventricular (LV) outflow tract obstruction are not candidates for operation. Furthermore, the intra- and early postoperative mortality rate for septal myectomy is 5 to 10%, and about 25% of patients do not receive satisfactory relief of symptoms during long-term postoperative follow-up study. As a result of these considerations, we began an intensive search for an alternative medical therapy for patients with this condition in 1977.

From the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland.

Address for reprints: Douglas R. Rosing, MD, Cardiology Branch, National Heart, Lung, and Blood Institute, Building 10 Room 7B-15, National Institutes of Health, Bethesda, Maryland 20205.

TABLE I Hemodynamic Effects of Verapamil

	Control	Verapamil Infusion (mg/kg/min) 0.007	0.014	0.021	SEM	F ratio (p value)
Heart rate (beats/min)	77 (61)	76 (61)	77 (38)	79 (23)	±14	0.18 (1.00)
Systolic blood pressure (mm Hg)	118 (62)	109* (62)	107* (40)	102† (25)	±17	6.88 (0.0002)
Mean pulmonary artery wedge pressure (mm Hg)	15 (56)	16 (55)	16 (37)	17 (23)	±6	1.01 (0.39)
Left ventricular end-diastolic pressure	18 (47)	17 (57)	18 (37)	17 (22)	±7	0.05 (1.00)
Cardiac index (liters/min/m^2)	2.4 (59)	2.4 (49)	2.5 (33)	2.5 (23)	±0.7	0.40 (0.76)

Statistical significance was determined by a 1-way analysis of variance.
Figures in parentheses indicate the number of patients in each group.
* $p < 0.005$.
† $p < 0.001$.
SEM = standard error of the mean.

TABLE II Effect of Verapamil on Outflow Tract Gradients

	Control	Verapamil Infusion (mg/kg/min) 0.007	0.014	0.021	SEM	F Ratio (p value)
Basal gradient (mm Hg)	62 (39)	47 (37)	44 (21)	29† (15)	±34	3.57 (0.02)
Maximal provokable gradient (mm Hg)	95 (24)	75 (22)	65* (12)	60* (8)	±37	2.93 (0.04)

Statistical significance was determined by a 1-way analysis of variance.
Figures in parentheses indicate the number of patients in each group.
* $p < 0.05$.
† $p < 0.01$.
SEM = standard error of the mean.

Because enhanced systolic function,[6] often leading to LV outflow tract obstruction,[7] and impaired diastolic function[6,8] are the characteristic hemodynamic features of patients with HC, it seemed to us that agents that decreased myocardial uptake of calcium might be helpful in improving these functional abnormalities. Kaltenbach et al's report[9] of symptomatic improvement in some patients with HC with the administration of the calcium antagonist verapamil provided further support for this approach. Because verapamil had been in general clinical use for 15 years, in 1977 we began administering this agent to our patients with HC. The primary purpose of this article is to review the experience with verapamil, as well as nifedipine, in treating patients with HC.

Hemodynamic Studies

Verapamil: Sixty-two patients received intravenous verapamil infusions at the time of cardiac catheterization performed after all cardiac medication had been discontinued for at least 5 half-lives. The mean age of the group was 44 years (range 21 to 70); 32 of the patients were men and 30 women. Thirteen patients had the nonobstructive form of the disease (basal or provokable LV outflow tract gradient ≤30 mm Hg). No patient had known significant coronary artery disease at the time of study. One patient was in atrial fibrillation and one had a demand ventricular pacemaker (VVI) in place. The remainder of the patients were in normal sinus rhythm at the time of study.

The effects of 10-minute drug infusions, at varying doses, on heart rate, systolic blood pressure, mean pulmonary artery wedge pressure, LV end-diastolic pressure, cardiac index and basal and provokable LV outflow tract gradients are shown in Tables I and II. Five patients had a verapamil-induced decrease in systolic blood pressure of ≥30 mm Hg and 2 of these patients had an increase in their basal gradients. No other patient had an increase in the gradient with verapamil administration. The effect of verapamil on outflow tract gradients was similar, independent of whether the gradient was provoked with a Valsalva maneuver, amyl nitrate inhalation or isoproterenol infusion. Twelve patients had a mean pulmonary artery wedge pressure >20 mm Hg at the time of control measurement. Figure 1 shows that verapamil administration produced a decrease in wedge pressure >2 mm Hg in 6 patients, resulted in no change (within ± 2 mm Hg) in 4, and caused a >2 mm Hg increase in 2. In 1 patient wedge pressure increased from 21 to 31 mm Hg

TABLE III Effects of Sublingual Nifedipine on Hemodynamic Features in 27 Patients

	HR (beats/min)	SBP (mm Hg)	PCW (mm Hg)	CI (L/min/M^2)	GRAD (mm Hg)	LVDV
C	78 ± 13	126 ± 15	15 ± 3	2.9 ± 0.8	56 ± 37	100%
N	91 ± 13*	103 ± 13*	17 ± 9	3.5 ± 0.8*	65 ± 43	131 ± 33%*

C = control; GRAD = basal subaortic left ventricular outflow tract gradient; HR = heart rate; LVDV = left ventricular end-diastolic volume; N = nifedipine; PCW = mean pulmonary artery wedge pressure; SBP = systolic blood pressure.
* $p < 0.005$.

and in another from 27 to 32 mm Hg. In 5 of 43 patients with a control mean pulmonary artery wedge pressure <20 mm Hg, verapamil resulted in an increase in pressure to >20 mm Hg (to 21, 22, 23, 24 and 35 mm Hg). Similar trends were observed in LV end-diastolic pressures.

In another article in this issue,[10] the effects of oral and intravenous verapamil administration on systolic and diastolic function, as measured by radionuclide angiography, are described in detail. Verapamil administration improved peak LV filling rate, time to peak filling rate, T time (time constant of LV pressure decrease after peak negative first derivative of LV pressure [dP/dt]), pressure-volume relation and contribution of rapid diastolic filling to overall LV filling. The LV ejection fraction decreased in response to intravenous verapamil but was unchanged when patients received it in short-term oral administration. Other investigators have found similar hemodynamic results with verapamil administration to patients with hypertrophic cardiomyopathy.[11–14]

Nifedipine: The hemodynamic effects of nifedipine administration resulted in a somewhat different trend compared with verapamil. Table III summarizes the effects of the short-term sublingual administration of 10 to 30 mg of nifedipine to 27 patients with no known coronary artery disease. Although the subaortic LV gradient did not decrease with nifedipine as it did with verapamil, there was an increase in cardiac output. The lack of change in gradient at a time when flow increased indicates that some decrease in LV outflow tract obstruction occurred. This effect may have been mediated by the increase in LV end-diastolic volume we observed,[15] although the mechanism by which diastolic filling increased is not clear. We found nifedipine exerted no effect on early diastolic filling, when measured by radionuclide angiography, during short-term oral administration (Table IV).[15] Filling improved when the same patients received oral verapamil; peak filling rate increased and time to peak filling rate decreased significantly when compared with the control situation (Table IV).

There is little additional information regarding the hemodynamic effects of nifedipine administration to patients with this disease. Lorell et al[16] observed that nifedipine administration improved diastolic function in a group of 10 patients, as did Senn et al[17] in a group of nonobstructive patients. Even less information is available regarding diltiazem administration to patients with HC. The only reported studies, by Nagao et al,[18,19] demonstrated that intravenous diltiazem decreased isovolumic LV relaxation time and bicycle exercise-

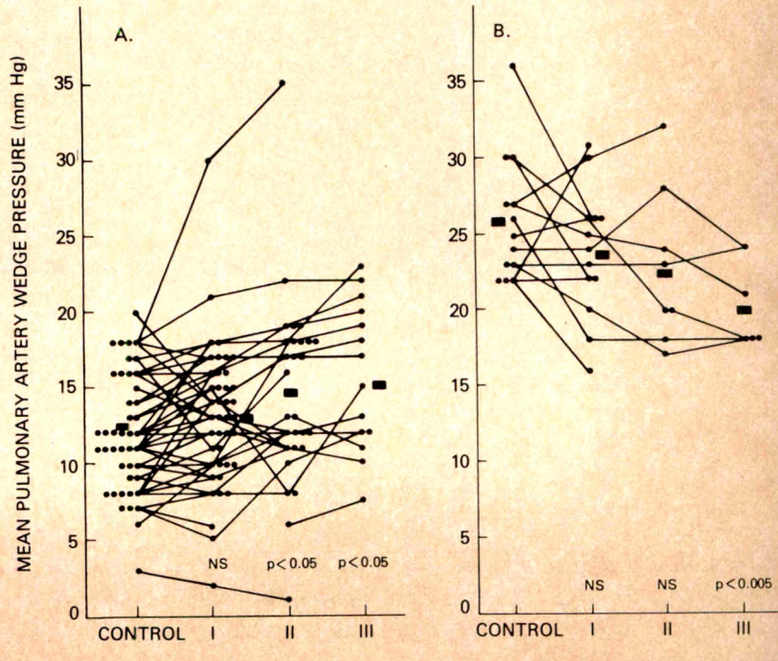

FIGURE 1. Response of mean pulmonary artery wedge pressure to verapamil infusions. Dose I = 0.007 mg/kg/min; II = 0.014 mg/kg/min; III = 0.021 mg/kg/min. Patients whose mean wedge pressures preverapamil were ≤20 mm Hg are displayed on **left,** and those whose preverapamil mean wedge pressures were >20 mm Hg are shown on **right. Horizontal bars** depict mean values for the group. P values represent comparisons with control values. F ratio for the left panel = 2.38 ($p = 0.07$), for the right panel = 2.98 ($p = 0.04$).

TABLE IV Nifedipine and Verapamil Effects on Left Ventricular Diastolic Function in 11 Patients

	PFR (EDV/s)	TPFR (ms)	HR (beats/min)	LVEF (c/o)
Control	3.2 ± 1.3	196 ± 32	77 ± 13	73 ± 11
Nifedipine	3.2 ± 1.1	192 ± 38	76 ± 11	71 ± 10
Verapamil	3.9 ± 1.2*	174 ± 32†	68 ± 8‡	72 ± 11

EDV = LV end-diastolic volumes; LVEF = LV ejection fraction; PFR = peak LV filling rate; TPFR = time to peak filling rate.
* $p < 0.02$ relative to control.
† $p < 0.05$ relative to control.
‡ $p < 0.002$ relative to control and nifedipine.

induced increases in pulmonary artery diastolic pressure.

Conclusion: The results of the hemodynamic studies indicate that intravenous verapamil, administered to patients with the obstructive form of HC, is capable of reducing LV outflow tract obstruction, as demonstrated by a decrease in LV outflow tract gradient with maintenance of cardiac output. The mechanism of this action appears to be both a decrease in systolic function, as shown by a decrease in the ejection fraction, and an increase in LV volumes produced by an enhancement of LV diastolic filling.[10] Although we have no data regarding the effect of long-term oral verapamil therapy on LV outflow tract obstruction, the work of Kaltenbach et al[20] would suggest that the oral administration of the drug also decreases LV outflow obstruction, and increases LV end-diastolic volume (10%) and stroke volume (11%). A preliminary report by Raff et al[21] described a 28% increase in LV end-diastolic volume without a significant change in end-diastolic pressure. We have demonstrated that after 1 year of verapamil therapy, the improvement in early diastolic function continues and, as in the short-term oral studies, the group as a whole still had no change in systolic function indexes.[10] However, the LV ejection fraction exhibited a persistent decrease (>5%) in individual patients. Kaltenbach et al[20] have also described a persistent negative inotropic effect (increased end-systolic volume and reduced peak LV systolic pressure) in 6 of 10 patients receiving long-term therapy.

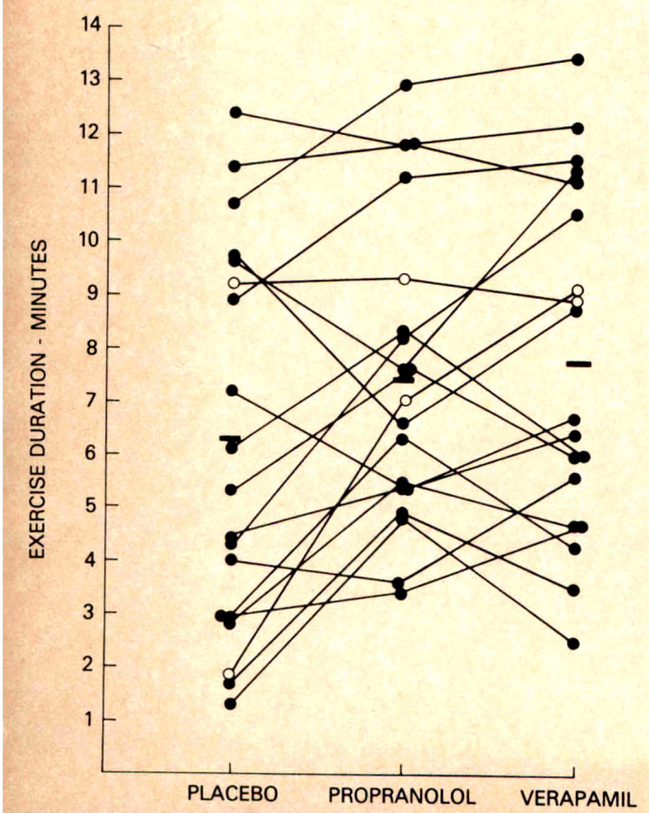

FIGURE 2. Effect of propranolol and verapamil administration on exercise capacity. **Horizontal bars** indicate mean values. **Closed circles** represent patients with obstructive hypertrophic cardiomyopathy; **open circles,** patients with nonobstructive disease. Reprinted with permission of American Heart Association.[22]

Thus, it would appear that the beneficial effects of the intravenous administration of verapamil to patients with HC result from a depression of systolic function and an enhancement of diastolic function. The salutory effects of long-term oral administration of the drug seem to be derived primarily from improved diastolic function with individual patients benefitting from decreased systolic function.

In the group of patients to whom we administered nifedipine, we could not demonstrate any consistent change in LV gradient or diastolic function. Although an increase in the calculated LV outflow tract orifice area may have occurred, LV systolic pressure remained increased, indicating that no decrease in LV wall stress occurred. Although our group data showed no hemodynamic benefit from nifedipine, there were isolated examples of significant decrease in LV outflow tract gradients and improvement in diastolic function. Moreover, Lorell,[16] Senn,[17] and their co-workers have described improved diastolic function in small groups of patients with the short-term administration of the drug.

Most of the foregoing descriptions and conclusions emphasize the effects of the calcium-channel blocking drugs in patients with the obstructive form of HC. However, the effects on filling pressures and diastolic function in subgroups of patients with nonobstructive disease or no basal LV outflow gradients appear to be the same.

Effects on Symptoms and Exercise Capacity

Short-Term Studies

Verapamil-propranolol-placebo: Treadmill exercise capacity and symptomatic status were evaluated

in 19 patients,[22] 17 of whom were New York Heart Association functional class III, despite taking what was considered to be optimal medical therapy. No patient had known significant coronary artery disease at the time of study. The other 2 patients were functional class II. Fifteen patients were taking propranolol at the time of admission to the study (median dose 320 mg/day), and 4 had been receiving the drug but had discontinued it. Verapamil, propranolol and placebo were administered in a double-blind randomized fashion.

Exercise capacity is depicted in Figure 2. With placebo, the average exercise duration was 6.1 ± 3.5 minutes. With verapamil, the average exercise time increased by 26 ± 35% (1.6 ± 2.2 minutes, $p < 0.005$), and with propranolol, it improved 21 ± 35% (1.3 ± 2.2 minutes, $p < 0.025$). There was no significant difference between the results with propranolol and verapamil.

Patients were also asked to identify the drug period during which they felt "best" and "worst," and 16 of the 19 patients were able to do this, sometimes selecting more than 1 period as "best" or "worst." With placebo, 7 patients felt "best" and 7 "worst," with verapamil it was 9 "best" and 4 "worst," and with propranolol 3 "best" and 7 "worst." Patient assessment of symptomatic response agreed with the results of exercise testing in 9 of 16 patients.

Verapamil-nifedipine-placebo: In a similar short-term, randomized, double-blind crossover study[23] comparing the exercise and subjective symptomatic responses of 27 patients with HC and no known coronary artery disease with 5 days each of placebo, verapamil and nifedipine treatment, we found that with placebo, maximal exercise capacity was 5.5 ± 3.3 minutes. With nifedipine there was a tendency for improvement as exercise time increased by 20 ± 47% to 6.6 ± 2.8 minutes ($p = 0.11$), whereas with verapamil a significant prolongation of exercise time, 38 ± 58%, compared with placebo, to 7.7 ± 3.3 minutes ($p = 0.02$) occurred.

In addition, 13 patients described their symptomatic response as "best" with verapamil, whereas 7 did the same for placebo, and 6 for nifedipine (a patient could choose more than 1 drug period as "best" or "worst"). Only 4 patients stated they felt "worst" with verapamil, compared with 7 for nifedipine and 12 for placebo. Four patients were removed from the study because of adverse "drug effects" (hypotension in 1 patient while taking verapamil and in 1 patient taking placebo, and syncope and pulmonary edema in 1 patient each while taking nifedipine).

Long-Term Clinical Effects

Subjective responses: Oral verapamil therapy was evaluated in 227 patients from September 1977 to June 1982. Thirteen patients had been taking verapamil therapy for 2 to 11 months when first evaluated by us. Six patients received 2 trials of verapamil therapy (in 4, before and after ventricular septal myectomy, in 2, before and after other medical therapy). The age range was 7 to 76 years (mean 48 ± 15); 129 were men and 98 women. One hundred seventy-nine patients had the obstructive form of HC; 54 had the nonobstructive form. Eighteen patients had undergone ventricular septal myectomy, and 11 of them still had the obstructive form of the disease. Verapamil therapy was begun in these patients either because of persistent symptoms or because of a return to an unacceptable quality of life after operation.

Twenty-two patients were in chronic atrial fibrillation at the onset of verapamil therapy. Coronary arteriography was performed in 81 of the 227 patients before the therapeutic trial. Fifty-eight patients had no significant coronary artery disease (>50% diameter luminal narrowing), whereas 9 patients had significant 1-vessel disease, 8 had double-vessel disease and 5 had triple-vessel disease.

At the time of initiation of verapamil therapy, 190 patients had been taking β-blocking drugs, whereas in

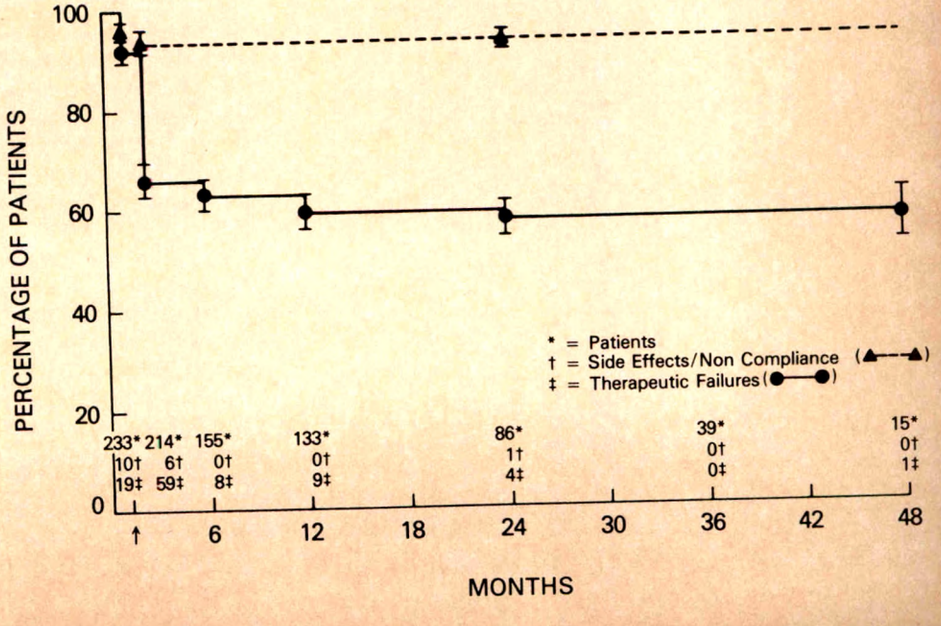

FIGURE 3. Plot of percentage of patients still taking verapamil after initiation of oral administration. Curves were obtained using method of Kaplan and Meier.[24] Upper curve (**broken line**) depicts those patients discontinuing verapamil because of adverse effects (16 patients) or noncompliance with protocol (1 patient). The lower curve shows all patients who discontinued drug independent of reason. Difference between curves is those patients in whom medication was stopped because of inadequate relief of symptoms (71 patients), death (9 patients) or loss to follow up (3 patients).

TABLE V Concomitant Cardiac Medication at Last Follow-up Visit

	Patients (n)
Diuretics	50
Antiarrhythmic drugs	28
Beta-blockers	12
Digoxin	3
Nitrates	2
Antihypertensive drugs	1

39 patients β blockers had been discontinued because of either lack of efficacy or adverse reactions. β-blocking drugs were discontinued when verapamil administration was initiated. Only 4 patients (1 with severe obstructive lung disease and 2 with diabetes) had never received β blockers. Despite receiving what was considered to be optimal medical therapy, 11 patients were classified as New York Heart Association functional class IV, 158 as functional class III, 58 as functional class II and 2 patients as functional class I (in 1 patient the indication for therapy was repetitive supraventricular tachycardia; in the other repetitive sustained ventricular tachycardia). Functional class could not be adequately defined in 4 patients; in each of these verapamil therapy had been begun before referral to the National Institutes of Health.

The maintenance verapamil dose in patients who tolerated this medication was 120 to 640 mg/day (median dose 360). One hundred thirty-three patients (59%) were still taking verapamil 3 to 53 months (mean 25 ± 13) after initiation of therapy. Three patients were lost to follow-up study—2 after taking verapamil 18 months without complaints, 1 with whom we could not make contact during the 10 months since discharge. Verapamil dose in the 133 patients still being actively followed has been 80 to 720 mg/day (median dose 360).

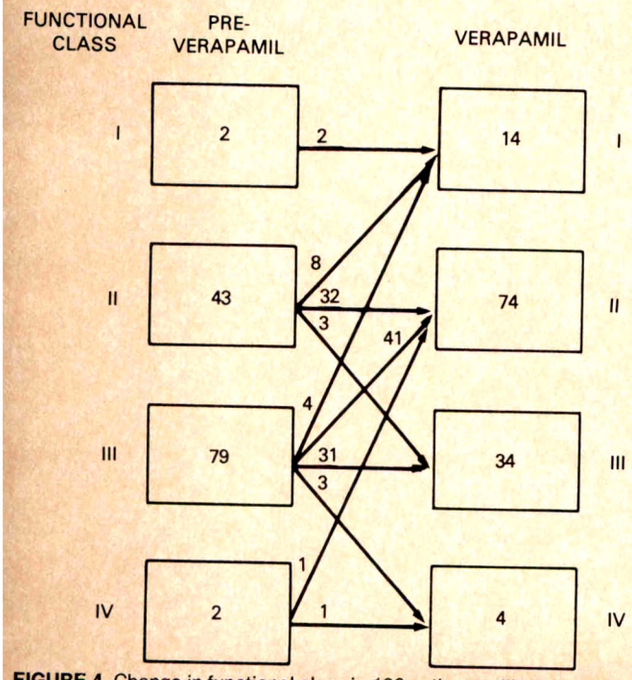

FIGURE 4. Change in functional class in 126 patients still taking verapamil. The patient group includes 2 patients lost to follow up, but whose functional class was known at time of last visit, 18 months after starting verapamil. Seven patients still taking verapamil are not included because their functional class could not be adequately defined either at time of initiation of verapamil therapy or at last follow up.

Among the 233 trials of verapamil therapy, the drug was stopped in 16 instances (7%) because of adverse drug effects and once because of a patient's inability to comply with the protocol. In 71 instances (30%), the drug was stopped because an acceptable quality of life was not obtained. Nine additional patients (4%) died while taking the drug. Three patients have been lost to follow up, and are counted as therapeutic failures. Figure 3 shows that all but 1 case of adverse effects and noncompliance occurred in the first 6 months after the initiation of therapy (59% occurred in the first month). Although 76% of the deaths and symptomatic failures occurred in the first 6 months of follow up, there is a consistent failure rate of 2.7% every 6 months thereafter. The patients with known coexisting coronary artery disease followed a course similar to the group as a whole, but long-term success was slightly reduced. Nine patients have remained with long-term verapamil therapy, 10 have undergone operation, 2 are taking other medication, and 1 has died.

The effect of verapamil therapy on functional class is shown in Figure 4. All 126 patients depicted have chosen to remain with verapamil therapy because of subjective symptomatic improvement or avoidance of adverse effects. We considered 5 of these to be therapeutic failures and surgery was recommended, but the patients chose to continue taking verapamil. Some of the patients required the addition or maintenance of other cardiac medication to achieve an acceptable lifestyle; these medications are listed in Table V.

Exercise testing: In 126 patients (including 11 with known coronary artery disease), a graded treadmill exercise test was performed with patients on no medication. Verapamil therapy was begun and the test was repeated in the hospital after the drug had been administered at least 5 days. This same procedure was performed 12 months later with 35 patients (1 with known coronary artery disease) and 24 months later with 32 patients (5 with known coronary artery disease). Table VI demonstrates that there was an initial improvement in exercise duration that was maintained at the time of follow up. Assessing the results of individual patients, and taking a 30% change in exercise duration as a definite change in exercise capacity, we found that 21% of patients had a further improvement over the long-term, 51% had a persistent improvement, and 28% had less of an improvement at their last outpatient test when compared with in-hospital values.

In 24 patients who had been taking verapamil for 1 year, exercise duration was determined after all medication had been stopped for 48 to 72 hours.[25] Although exercise duration without medication 1 year after the start of verapamil therapy was greater than before therapy was begun (8.3 ± 1.1 versus 6.7 ± 0.8 minutes), the difference did not achieve statistical significance. Figure 5 shows that 12 patients had an improved base-

TABLE VI Exercise Duration

Patients (n)	Exercise Time (minutes)			
	Without Medication	With Verapamil		
		In Hospital	12 Months	24 Months
126	6.0 ± 4.0	8.4 ± 4.5*	...	...
35	6.6 ± 3.6	9.2 ± 4.5†	8.5 ± 4.3‡	...
32	6.5 ± 3.8	9.2 ± 4.2*	...	9.1 ± 4.6*

Compared with time achieved without any cardiac medication.
* $p < 0.001$.
† $p < 0.01$.
‡ $p < 0.02$.

line exercise performance after taking the drug for 1 year, 8 had no change, and 4 had a decrease in baseline capacity.

Echocardiographic studies: In 32 patients who were maintained with verapamil because they achieved an acceptable quality of life, M-mode echocardiographic studies were performed according to techniques described previously[25] before starting verapamil and at an average follow-up time of 39 ± 8 months (range 24 to 53). Two of these patients had known coronary artery disease. Figure 6 demonstrates the results. Ventricular septal thickness was 22.2 ± 3.6 mm before verapamil administration and was reduced to 20.7 ± 4.0 mm ($p < 0.005$) at the time of last follow-up study. LV posterior wall thickness was 12.0 ± 2.0 mm before verapamil administration and 12.8 ± 2.5 (p = NS) at last follow up.

Nine patients had a change in ventricular septal thickness of ≥4 mm; in 8 it decreased, in 1 it increased. Two-dimensional echocardiograms were available for both studies in all 9 patients and were analyzed to try to determine whether the change in thickness measured on M-mode echocardiography was real or whether it could be ascribed to small alterations in transducer angulation that detected adjacent areas of left ventricle with different degrees of hypertrophy. This could produce an apparent, but not real, change in thickness if localized areas of thickening or thinning existed such that a slight change in the direction of the M-mode beam could move the beam from a relatively thick to a relatively thin area or vice versa. Apparent changes might also be detected if an echocardiogram was not of optimal quality, insofar as septal edges might not be properly identified. The analysis of the 2-dimensional studies indicated that the decrease in thickness appeared real in 2 patients, could be real or due to LV hypertrophy distribution in 2, were probably due to distribution of hypertrophy in 2 and were probably due to distribution or quality in 2. No patient had evidence of a myocardial infarction. In the 1 patient with an increase in thickness, it appeared to be due to LV hypertrophy distribution. Thus, the change appears to be real in 4 of 8 patients who had a decrease in septal thickness ≥4 mm, or in 13% (4 of 32) of the patients studied after verapamil treatment for a mean of 39 months.

Conclusions: The results of these investigations indicate that verapamil improves exercise capacity and

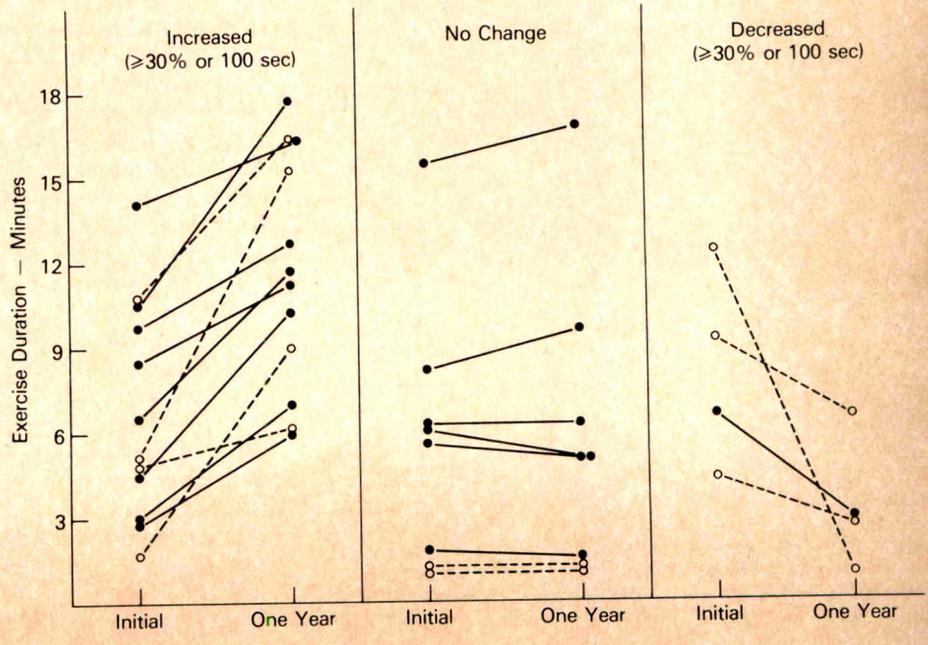

FIGURE 5. Exercise capacity of patients taking no cardiac medication before starting therapy with verapamil (initial) and 1 year later without cardiac medication after verapamil had been discontinued for 48 hours (1 year). **Left,** 12 patients had an increase in exercise capacity that could not be ascribed to variability inherent in testing technique and thus was considered significant. **Center,** 8 patients had no change; **right,** 4 patients had a significant decrease in exercise capacity greater than would be expected by random variation. **Open circles** and **broken lines** depict standard protocol exercise test and **closed circles** and **solid lines** depict augmented protocol exercise test. Reprinted with permission from *Am J Cardiol.*[25]

TABLE VII Incidence of Adverse Effects*

	Hospital	Duration of Treatment (months)					
		0–5	6–11	12–23	24–35	36–47	≥48
Patients	233	214	155	133	86	39	15
Cardiovascular	12	4	4	3	2	0	2
Pulmonary congestion	6	3	4	1	2	...	1
Hypotension	8	1	...	2	...	...	1
Electrophysiologic	31	1	1	0	1	1	0
Sinus arrest	5	...	...	...	...	...	...
Atrioventricular block							
Junctional rhythm	20	1	...	...	1	1	...
Ventricular rhythm	1	...	...	...	...	...	...
Wenckebach	5	...	1	...	...	...	...
Other	8	14	40	17	8	3	1
Abdominal discomfort	1	3	2	1	1	...	...
Constipation	5	5	13	7	4	...	...
Vision disturbance	...	1	...	...	...	...	...
Headache	2	2	1	1	1	...	...
Hair loss	...	...	1	1	1	...	...
Depression	...	...	1	...	1	...	...
Edema	...	1	19	6	...	2	1
Irritability	...	1	1	...	...	...	...
Impotence	...	...	1	1	...	1	...
Rash	...	1	1	...	...	...	...
Discontinued because of adverse effect	9	4	2	0	1	0	0

* Some patients had >1 adverse effect.

subjective symptoms during short- and long-term therapy in a group of patients with HC who previously had had an inadequate symptomatic response to conventional therapy with β-receptor blocking agents. These findings are similar to other long-term studies with verapamil.[20,26–28] In our patients, control hemodynamic findings, control exercise studies with patients not taking medication and initial improvement in exercise time shortly after verapamil was begun were not helpful in discriminating between those patients who were going to derive significant long-term clinical benefits from drug administration and those who were not.

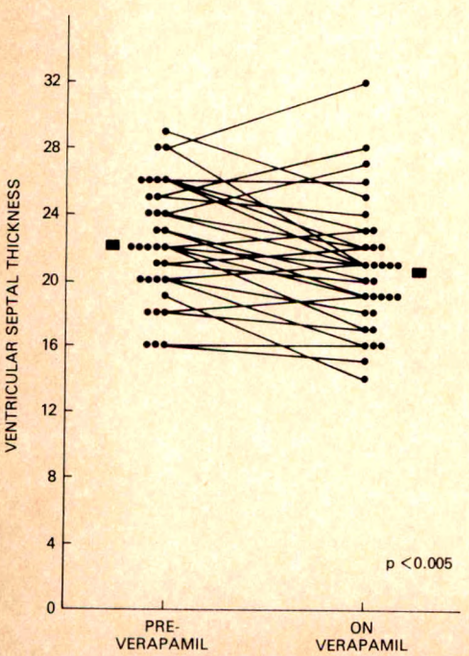

FIGURE 6. Echocardiographic measurements of ventricular septal thickness at time of last follow up in 32 patients who had been taking verapamil therapy for at least 24 months. **Horizontal bars** depict mean values.

Although verapamil produced no consistent changes in the patients' underlying functional capacity (exercise without any medication), 12 of 24 patients had an improved baseline exercise capacity that could not be ascribed to variability in the testing technique.[25] This improvement could have been caused by a training effect caused by a general increase in physical activity secondary to a more effective control of symptoms. Alternatively, it is intriguing to postulate that these 12 patients had an improvement in the underlying intrinsic cardiomyopathic process. Although ventricular septal and LV free wall dimensions were unchanged at 1 year,[25] a decrease in septal wall thickness was noted in a larger group followed for a longer period of time. Other investigators have reported similar findings in patients taking verapamil.[27–29]

Nonetheless, at this time it would be unjustified to conclude that verapamil alters the course of the basic disease process. Not only could the improved baseline exercise capacity be due to a training effect, but the biological significance of the 1.5 mm decrease in septal thickness is unknown. This latter finding must also be considered in the context of the fact that 2-dimensional echocardiographic studies have demonstrated the heterogeneous distribution of hypertrophy in these patients,[30] thus raising the question of whether M-mode echocardiography is a reliable technique for measuring changes in wall thickness in this disorder. Although the results of 2-dimensional echocardiography studies suggest that some patients have a real decrease in septal thickness while taking verapamil, no echocardiographic measurements in a control group of patients with HC

exist to compare with the apparent changes produced by verapamil.

Finally, even if such changes represent a significant verapamil-induced decrease in hypertrophy, they could be explained by a decrease in LV outflow obstruction and LV systolic wall stress reducing the stimulus for LV hypertrophy. Further work with 2-dimensional echocardiography or other imaging techniques and the use of control groups will be necessary to determine the significance of these exercise and echocardiographic findings.

No information is available at present regarding the effects of long-term nifedipine or diltiazem treatment of patients with HC.

Adverse Effects

Intravenous administration: Five of the 62 patients who received intravenous verapamil suffered an adverse electrophysiologic effect from the drug. Four patients had atrioventricular dissociation with a narrow QRS escape rhythm and 1 patient had Wenckebach block after PR prolongation to 0.40 seconds. All but 1 patient remained in a stable hemodynamic state and had the return of sinus rhythm within the few hours after discontinuation of the drug infusion. The 1 exception required ventricular pacing and phenylephrine infusion for several hours after leaving the catheterization laboratory.

Long-term oral administration: As described previously, most of the significant, potentially life-threatening adverse effects occurred early in the course of treatment. Table VII demonstrates that the most common were electrophysiologic and consisted of 24 patients who had atrioventricular dissociation (junctional escape rhythm in 23 and a ventricular escape in 1), 5 who had sinus arrest and 6 who had Wenckebach heart block. These effects disappeared with a decrease in dosage, and the majority of these patients continued taking verapamil; in 2, placement of a pacemaker was required. Seventeen patients had pulmonary congestion with verapamil whereas 12 others had significant, usually postural, hypotension. Thirteen of the 17 patients with pulmonary congestion had ≥50 mm Hg basal or provokable LV outflow tract gradients. The drug was stopped because of the development of pulmonary congestion in 4 of these patients; 3 others died while taking verapamil. The other 10 patients continued taking the drug, but had diuretics added to their treatment. Those with hypotension usually tolerated a decrease in dose. In 12 of these 59 patients who had serious adverse cardiovascular effects from verapamil administration, it was necessary to discontinue the drug; 3 others died while taking the drug. This represents 7% of the patients begun with verapamil therapy and includes 4 patients with adverse electrophysiologic effects, the 4 with pulmonary congestion and 2 with postural hypotension.

Included in this list of significant adverse drug effects are 4 patients who suffered adverse effects due to the administration of the combination of verapamil and quinidine. This figure represents 15% of the 27 patients taking both drugs. Three of these patients had severe

TABLE VIII Patient Deaths With Verapamil Therapy

Patient Initials	Age (yr) & Sex	History	PAW	LVOT Gradient	Time on Verapamil	Verapamil Dose/Day (mg)	Other Medications	Cause of Death
HLG	55M	CAD-CABG	10	Obst → Non (Oper)	18 months	640	Metoprolol, isosorbide dinitrate	Sudden, probable coronary death*
MMB	47F	. . .	. . .	Obst	26 months	360	Quinidine	Cancer of colon (better on verapamil)
FRK	40M	Pulmonary edema	26	62 (73)†	2 months	360	. . .	Pulmonary edema
MLE	34F	Orthopnea		100	11 months	480	. . .	Pulmonary edema
FBK	57M	. . .	12	Obst → Non (oper)	18 months	240	. . .	Therapeutic failure, cardiac arrest
WAG	51M	SOB at rest	14	110	2 days	480	. . .	Hypotension, pulmonary edema, renal failure
FFR	72M	Hypertension, renal failure	. . .	Obst	4 months	320	Methyldopa, furosemide	Hypertensive crisis → cerebrovascular accident
RO	41M	Heart failure	30	Non	7 months	320	Furosemide, quinidine	Heart failure
DRM	26M	Dilated LV, Low LVEF	14	Non	3 weeks	240	. . .	Sudden, probable arrhythmia

* Also had triple-vessel coronary artery disease.
† Provoked gradient.
CABG = coronary artery bypass graft; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; Non = nonobstructive; Obst = obstructive; Oper = myectomy; PAW = pulmonary artery wedge pressure; SOB = shortness of breath.

postural hypotension with pulmonary edema developing in 2. The fourth patient had recurrent presyncope and syncope. Although this latter occurrence could have been the result of quinidine syncope or underlying disease, we have included it as an adverse reaction secondary to combination verapamil-quinidine therapy causing postural hypotension because presyncope and syncope decreased in frequency with the discontinuation of quinidine, and had not occurred when quinidine was administered alone before verapamil treatment. The mechanism presumed responsible for the adverse effect of combined quinidine-verapamil administration is a potentiation of verapamil's hypotensive action by the α-blocking effect of quinidine.[31] Two of the patients returned to long-term verapamil therapy alone without adverse effects.

Although we have included the occurrence of pulmonary congestion and postural hypotension as adverse effects of verapamil (or of verapamil and quinidine) therapy, it is possible that these adverse effects occurred *despite* verapamil therapy. This may be especially true in the 12 patients who had these occurrences after having taken verapamil for $\geq$1 month, compared with the 15 who had pulmonary congestion or hypotension soon after starting verapamil.

Less serious adverse effects occurred more frequently than the aforementioned adverse effects, but required cessation of treatment in only 4 patients, 1 each with upper gastrointestinal complaints, hair loss, vision disturbances and facial edema. Other types of adverse nuisance effects and their frequency are listed in Table VII.

Deaths: Nine patients died while taking verapamil therapy (Table VIII). Although the deaths in patients MMB, HLG, FBK, RO and FFR probably occurred *despite* verapamil therapy, the situation in the other 4 patients is not as certain. We have previously discussed how verapamil could initiate a series of electrophysiologic or hemodynamic events or both resulting in hypotension and, in patients with LV outflow tract obstruction, increased LV obstruction.[32] If the hypotension or increased obstruction or both is prolonged, decreased myocardial perfusion and pulmonary edema or cardiac arrest could result. Whether such events caused or contributed to the deaths of MLE, WAG, FRK and DRM is uncertain, but remains a reasonable possibility.

There are no available investigations examining the long-term effects of other calcium-channel blockers in this disease, so the incidence and types of adverse reactions are unknown. In our limited experience with nifedipine, we have seen the occurrence of pulmonary congestion and hypotension. Electrophysiologic problems with nifedipine should not occur, but given the known electrophysiologic effects of diltiazem,[33] adverse actions on the sinus and atrioventricular nodes similar to those described with verapamil can be anticipated.

In summary, verapamil offers an important alternative to β-blocker therapy in patients with HC. Nifedipine does not appear to have as beneficial hemodynamic or clinical effects in these patients, but has been found to be helpful in some patients with this disease; thus, it is reasonable to try nifedipine therapy in patients who have failed or do not tolerate verapamil. There are insufficient data on the efficacy of diltiazem, of combined calcium-channel and β-blocker therapy, or of combined calcium-channel–blocker therapy in these patients to draw any conclusions as to their value.

Because verapamil may cause serious complications in patients with HC, we have adopted the following policy regarding its administration to these patients. If alternative therapy is available, the drug is probably contraindicated in patients who have (1) increased pulmonary capillary wedge pressure (>20 mm Hg) in the presence or absence of obstruction of LV outflow, (2) a history of paroxysmal nocturnal dyspnea or orthopnea in the presence or absence of obstruction to LV outflow, (3) sick sinus syndrome without an implanted pacemaker, (4) significant atrioventricular junctional disease without an implanted pacemaker and (5) low systolic blood pressure, particularly in the presence of LV outflow obstruction. The drug should be given with caution to patients with systolic hypertension and marked obstruction to LV outflow, and moderate prolongation of the PR interval (>0.26 seconds) on the electrocardiogram. The same policy is followed regarding nifedipine administration, except for the caveats concerning electrophysiologic complications.

Because clinical findings do not always correlate with the measurement of mean pulmonary wedge pressure, we perform a right heart catheterization in all patients who are candidates for calcium-channel blocker therapy, and who have not had a recent catheterization (within 6 months) or who have had a worsening of symptoms since their last catheterization. If a mean wedge pressure >20 mm Hg is present, we usually will use other forms of treatment. It is not customary to administer the calcium-channel blocker in the laboratory for we have not found the short-term effects to be helpful in predicting the long-term effects of drug administration. In those patients who have significant increases in their mean pulmonary artery wedge pressure or evidence of atrioventricular or sinus node disease, we often do administer the calcium-channel–blocker in the catheterization laboratory to be sure the drug will not exacerbate these abnormalities. We only begin in-hospital drug therapy in those patients who are identified as being at relatively higher risk for having an adverse effect from their treatment.

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Therapeutic Application of Calcium-Channel Antagonists for Pulmonary Hypertension

MILTON PACKER, MD

Calcium-channel antagonists may provide an effective approach to the treatment of pulmonary hypertensive disorders. Biochemical evidence suggests that pulmonary vasoconstriction results from the transmembrane flux of calcium into vascular smooth muscle; accordingly, the pulmonary pressor responses in experimental hypoxic pulmonary hypertension can be attenuated by verapamil and nifedipine. In patients with chronic obstructive lung disease, nifedipine decreases pulmonary artery pressures and pulmonary vascular resistance in proportion to the severity of hypoxemia before treatment. However, little pulmonary vasodilator effect is seen when hypoxemia is corrected by inhalation of oxygen, and systemic arterial oxygen desaturation can occur after nifedipine in patients breathing room air; most importantly, long-term studies in patients with chronic lung disease are lacking. In selected patients with primary pulmonary hypertension and other obliterative diseases of the pulmonary vasculature, nifedipine produces short- and long-term hemodynamic improvement at rest and during exercise, and these benefits are frequently paralleled by amelioration of dyspnea and fatigue. However, in patients in whom right ventricular function has been severely compromised by chronic pressure overload, both verapamil and nifedipine may exert notable depressant effects on right ventricular performance, despite the decrease in right ventricular afterload that would be expected to accompany a decrease in pulmonary vascular resistance. These negative inotropic actions may result in serious deleterious clinical reactions.

Although calcium-channel antagonists represent a promising approach to the management of patients with pulmonary hypertension, the long-term efficacy and safety of these drugs in this disorder remain to be established. (Am J Cardiol 1985;55:196B–201B)

Cor pulmonale consequent to long-standing pulmonary hypertension is a major cause of cardiovascular morbidity and mortality.[1] The obstruction to pulmonary blood flow in this disorder is principally the consequence of obliterative changes in the pulmonary vasculature, resulting from either a primary process within the pulmonary arteries or secondary to pulmonary parenchymal disease.[2,3] However, there is considerable evidence that the severity of the pulmonary hypertensive state may be exacerbated to varying degrees by reversible pulmonary arteriolar constriction.[4] This appears to be particularly true in patients with hypoxic pulmonary hypertension, in whom pulmonary vascular resistance may decrease dramatically after oxygen inhalation and who may benefit clinically from long-term oxygen therapy.[5]

Based on such encouraging results, several investigators suggested that attempts to dilate the pulmonary vasculature directly by the administration of vasodilator drugs might be therapeutically useful in the treatment of patients with pulmonary hypertension regardless of the underlying cause. Isolated reports of benefit have appeared with the use of α-adrenergic antagonists,[6,7] β-adrenergic agonists[8] and direct-acting vasodilator drugs[9–11] in both primary and secondary pulmonary hypertensive states. In many of these patients, the pulmonary vasculature seemed to be exquisitely responsive to pharmacologic interventions, and some of these persons had substantial hemodynamic and clinical improvement from long-term vasodilator therapy. Unfortunately, attempts to expand this therapeutic approach to a large number of patients have produced disappointing results; in subsequent trials, patients frequently failed to benefit, and serious adverse reactions were common.[12–14] Hence, the search continues for vasodilator agents that might prove to be more ef-

From the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine of The City University of New York, New York. This study was supported in part by Young Investigator's Research Award, R23-HL-25055, from the National Heart, Lung and Blood Institute, the National Institutes of Health, Bethesda, Maryland.

Address for reprints: Milton Packer, MD, Division of Cardiology, Mount Sinai Medical Center, 1 Gustave Levy Place, New York, New York 10029.

fective and better tolerated than presently available drugs.

Because vasoconstriction is ultimately mediated by the intracellular interaction of calcium with myofibrillar elements within the vascular smooth muscle cell,[15] the use of drugs that block the transmembrane influx of calcium may provide a specific and effective approach to the treatment of pulmonary hypertension. This report reviews the evidence for and against the use of calcium-channel antagonists in primary and secondary pulmonary hypertensive disorders.

Theoretical Basis for Use of Calcium Antagonists in Treatment of Pulmonary Hypertension

Biochemical evidence: The potential usefulness of calcium antagonists in the treatment of patients with pulmonary hypertension is based on a number of independent lines of evidence that suggest that calcium plays a key role in the pathogenesis of pulmonary vasoconstriction. Biochemical studies in animals with chronic hypoxic pulmonary hypertension indicate that hypoxia causes a shift of calcium from extra- to intracellular sites.[16] With a decrease in ambient oxygen, the vascular smooth muscle cell accumulates calcium and contracts; this occurs because anaerobic glycolysis produces sufficient energy substrates to support contraction but not to maintain a transmembrane ionic gradient.[17,18] Consequently, the cell membrane depolarizes, leading to the influx of extracellular calcium, and, as the cytoplasmic levels of calcium increase, smooth muscle contraction occurs.[19] Hence, hypoxia causes pulmonary vasoconstriction by directly acting to depolarize the vascular smooth muscle cell and initiate transmembrane entry of calcium.[20–22] Accordingly, the administration of a calcium-channel antagonist may lead to pulmonary vascular relaxation by blocking the entry of *extra*cellular calcium.[19] The effects of calcium-channel blockage are in contrast to those of other pulmonary vasodilators, which appear to act exclusively on the *intra*cellular calcium pool, either by enhancing intracellular sequestration or by increasing extrusion of activator calcium.[19,23]

Experimental models of hypoxic pulmonary hypertension: Experimental models of pulmonary hypertension support the biochemical evidence suggesting that calcium plays an important role in mediating pulmonary vasoconstriction. In isolated, artificially perfused and ventilated rat lungs, McMurtry et al[24] showed that alveolar hypoxia produced an immediate and marked pulmonary hypertensive response, which was blocked by verapamil; a similar inhibitory effect was seen with nifedipine in isolated pig lungs by Kennedy and Summer.[25] In both studies, attenuation of pulmonary vasoconstriction occurred in a dose-dependent fashion, such that nearly complete abolition of the pulmonary pressor response to hypoxia was observed with high doses of both calcium-channel antagonists.

These findings were subsequently extended by several investigators to the intact animal. Tucker et al[23] showed that verapamil attenuated the pulmonary hypertensive effects of hypoxia in anesthetized dogs, and similar findings were observed with nifedipine in the same species by Young,[26] Bishop[27] and their co-workers. Young et al[26] studied the effects of equimolar concentrations of nifedipine, verapamil and diltiazem on hypoxic pulmonary hypertension in the anesthetized dog. They noted that nifedipine decreased pulmonary vascular resistance without a change in pulmonary artery pressures, and this beneficial effect was seen only during conditions of hypoxia; nifedipine exerted no pulmonary vasodilating effect when alveolar oxygen content was restored to normal. In contrast, verapamil and diltiazem exerted no vasodilating effects on the pulmonary circuit in this study regardless of the inhaled oxygen concentration. The lack of efficacy of verapamil and diltiazem was likely the result of the low doses used (all drugs were administered in equimolar rather than equipotent concentrations). When higher doses of verapamil were used in subsequent studies, its pulmonary vasodilating effects were found to be comparable to those of nifedipine.[28] All of these observations indicate that calcium-channel antagonist can exert selective dilating effects on the pulmonary vasculature and that these actions are preferentially exerted in states characterized by high vasoconstrictor tone.

The ability of calcium-channel antagonists to inhibit the pulmonary hypertensive response to stimuli other than hypoxia remains controversial. McMurtry et al[24] noted that verapamil exerted minimal effects on the pressor response to angiotensin II or prostaglandin $PGF_{2\alpha}$ in the isolated rat lung; they also observed a similar specificity for hypoxic stimuli in the anesthetized dog.[23] To explain these findings, the investigators suggested that prostaglandins mediated their pulmonary vasoconstrictor effects by acting on intracellular calcium stores, and, thus, their pressor responses were unaffected by drugs that acted at the cell membrane.[19,23] However, it is unclear whether such a simple conceptual model is valid, particularly in view of recent evidence that verapamil and nifedipine can inhibit prostaglandin-mediated pulmonary vasoconstriction.[26,28] There appear to be a number of mechanisms that may account for the attenuation of pulmonary vasoconstriction by calcium-channel blockade regardless of the site of action of the inciting stimulus. As stated earlier, verapamil and nifedipine may be effective because a stimulus acts directly to depolarize the smooth muscle cell and initiate transmembrane calcium influx.[20–22] Alternatively, calcium-channel antagonism may abolish the constrictor response by inhibiting the release of a humoral intermediate from secretory cells in the perivascular tissues,[29,30] because extracellular calcium plays a key role in excitation-secretion coupling.[31] Lastly, even if a substance exerts its pulmonary vasoconstrictor effects entirely by way of an action on intracellular calcium stores, calcium-channel blockade may depress the rate at which intracellular stores of calcium are replenished from extracellular sources, and, therefore, may interfere indirectly with the observed vasoconstrictor response.[32]

In contrast to the dramatic responses of verapamil and nifedipine in hypoxic pulmonary vasoconstriction of short duration (<1 hour), the effectiveness of calcium-channel blockade in experimentally induced

chronic hypoxic pulmonary hypertensive states is less clear. Verapamil's ability to attenuate the vasoconstrictor response to acute hypoxia may become progressively less marked with repeated hypoxic exposures.[23] This may explain why in unanesthetized calves confined in a hypoxic environment for 2 weeks, administration of verapamil produced only modest decreases in pulmonary artery pressure and pulmonary vascular resistance, and these pulmonary vasodilator effects were less marked than those seen with oxygen or after administration of a β-agonist agent.[33] These findings suggest that in pulmonary hypertensive states of long duration, biochemical changes may occur that limit the magnitude of vasodilation that can be achieved by calcium-channel blockade. If calcium is located primarily intracellularly in chronic hypoxic pulmonary hypertension,[16] the administration of drugs that act at the cell membrane may have little effect on the vasoconstricted state compared with agents that affect intracellular calcium transport (for example, β-adrenergic agonists).[19,33] In studies of long-term treatment with verapamil administered prophylactically to rats confined in a hypoxic atmosphere for 3 to 4 weeks, drug-treated subjects had less marked increases in pulmonary artery pressure and less pronounced hypertrophy of the right ventricle than did control rats, but the magnitude of observed benefit was small.[34,35] With more prolonged periods of hypoxia (comparable to those seen clinically), structural obliterative changes may take place within the pulmonary vessel walls from prolonged vasoconstriction[36]; these may result in irreversible obliterative changes in the pulmonary vasculature, which then become unresponsive to any pharmacologic intervention.[37,38]

Clinical Application of Calcium Antagonists in Patients with Pulmonary Hypertension

Hypoxic pulmonary vasoconstriction in chronic obstructive lung disease: Because calcium-channel blocking drugs proved efficacious in acute experimental hypoxic pulmonary vasoconstriction, verapamil, nifedipine and diltiazem were subsequently administered to patients with hypoxic pulmonary hypertension in an effort to achieve similar favorable hemodynamic results.[39–41] Simonneau et al[40] administered 20 mg of nifedipine sublingually to 13 patients with chronic obstructive pulmonary disease who had severe hypoxemia secondary to acute respiratory failure. While these patients were breathing room air, nifedipine produced a marked decrease in mean pulmonary artery pressure and pulmonary vascular resistance associated with a mild increase in cardiac output. The magnitude of the decrease in pulmonary vascular resistance correlated inversely with the control arterial oxygen tension; little pulmonary vasodilation was observed in patients whose control oxygen pressure was greater than 60 mm Hg. When oxygen tension was increased by breathing oxygen, pulmonary arterial pressure and pulmonary vascular resistance decreased to the same extent as with nifedipine, and there was no additional effect when nifedipine was added to oxygen therapy.

Preliminary work by Kennedy et al[42] indicates that nifedipine produces beneficial effects in hypoxic pulmonary hypertension in patients with chronic obstructive pulmonary disease who are clinically stable and not in acute respiratory failure. In a double-blind, placebo-controlled, crossover study, nifedipine decreased pulmonary vascular resistance at rest and attenuated the increase in pulmonary vascular resistance during exercise in 5 patients while they were breathing room air, but exerted little additional benefit when added to oxygen therapy. Similar hemodynamic responses to nifedipine were seen in patients with chronic obstructive lung disease studied by El Allaf,[43] Muramoto[44] and their co-workers.

Although encouraging, these results need to be interpreted cautiously. Investigators have long feared that the administration of pulmonary arterial dilating drugs to patients with secondary hypoxic pulmonary hypertension might lead to systemic hypoxemia.[6,7,14,45] This fear was based on the theory that the pulmonary vessels most likely to be pharmacologically responsive to vasodilator stimuli were those in which local hypoxia-mediated vasoconstriction prevented perfusion of hypoventilated alveoli; dilatation of these vessels could lead to significant venous admixture and decrease in systemic oxygen saturation.[45] It is of interest, therefore, that, in the studies of Simonneau,[40] Kennedy[42] and their co-workers, arterial oxygen tension decreased significantly with nifedipine, and was not reversed by oxygen administration. This is consistent with the concept that arterial desaturation is the result of transpulmonary shunting of blood through poorly ventilated alveoli. However, in both studies, oxygen transport to the peripheral tissues increased after nifedipine, because nifedipine therapy was accompanied by a significant increase in cardiac output. This is in contrast to the effects of nitrates in patients with chronic obstructive lung disease, which fail to increase cardiac output, and thus produce significant decreases in arterial tension and oxygen transport in patients with hypoxic pulmonary hypertension.[45]

Unfortunately, none of these early studies evaluated the long-term effects of calcium-channel blockade in patients with hypoxic pulmonary vasoconstriction. Although sustained amelioration of pulmonary hypertension can be obtained by 24-hour continuous-flow oxygen therapy,[5] it is not clear that similar long-term benefits will accompany the administration of nifedipine or other calcium-channel antagonists, even though the short-term effects of these agents are similar to those seen with oxygen.[40] Whereas oxygen therapy may produce long-term effects that exceed in magnitude the short-term responses,[33] the benefits of vasodilator therapy frequently diminish with time.[46] Resolution of these dilemmas awaits results for long-term hemodynamic studies and randomized clinical trials.

Primary pulmonary hypertension: Reports of the favorable effects of calcium-channel blockade in patients with hypoxic pulmonary hypertension have led to the application of these drugs to the treatment of patients with pulmonary hypertension of unknown

cause (primary pulmonary hypertension). Although the pathophysiologic factors that underlie the development of pulmonary hypertension in these patients remain unknown, the obliterative vascular lesions that characterize this disorder have long been thought to arise secondarily to abnormal pulmonary vasoconstriction.[37,47] Consequently, a number of vasodilator drugs have been administered to these patients in an attempt to attenuate the vasoconstrictive components of the disease and to forestall the development of irreversible vascular sequelae.[48] Although a variety of vasodilator drugs have been advocated for use in this disorder,[4,8,9,11,49] none has proved to produce consistent hemodynamic and clinical benefits.[12–14] The most serious disadvantage of this therapeutic approach is that most vasodilator drugs produce systemic vasodilation that is greater in magnitude than the degree of pulmonary vasodilation.[14] Under such circumstances, systemic vasodilation might occur without an increase in cardiac output and lead to severe hypotension;[14] on the other hand, if the cardiac output increases markedly in the absence of a comparable pulmonary vasodilator effect, pulmonary hypertension can be exacerbated.[48]

In contrast to traditional vasodilator therapy, however, calcium-channel antagonists appear to exert selective dilator effects on the pulmonary circulation and are preferentially active in vasoconstrictive states.[15,50,51] Hence, they might be particularly beneficial in the management of patients with primary pulmonary hypertension and other obliterative pulmonary vascular diseases. Theoretically, of the available agents, verapamil has particular appeal, because this drug exerts less marked effect on the systemic circulation than does nifedipine,[52] and thus may produce less hypotension than do drugs with pronounced systemic vasodilator actions.

A number of investigators have reported favorable effects of calcium-channel blockade in patients with primary pulmonary hypertension.[53–58] In a series of case reports, calcium-channel antagonism increased cardiac output and decreased pulmonary artery pressure and pulmonary vascular resistance at rest and during exercise; these hemodynamic effects were sustained for 2 to 6 months and were associated with an amelioration of symptoms of dyspnea and signs of right-side heart failure. Camerini et al[53] first reported the beneficial effects of nifedipine in a patient with primary pulmonary hypertension; nifedipine (100 mg daily) produced marked increases in cardiac output and decreases in mean pulmonary artery pressure and pulmonary vascular resistance, which were sustained for 3 months and were associated with marked symptomatic improvement. Similar short- and long-term hemodynamic and clinical effects were observed by De Feyter et al[54] in a patient who received treatment with nifedipine, 120 mg daily for 6 months. Saito et al[56] claimed to have observed beneficial effects with nifedipine, 30 mg daily for 1 year, in a patient in whom cardiac catheterization during therapy showed marked resolution of pulmonary hypertension compared with a previous catheterization performed 2 years earlier; however, the short-term effects of nifedipine were not assessed. Wise et al[55] reported on a patient with primary pulmonary hypertension in whom nifedipine, 40 mg daily, produced a marked increase in cardiac output and decrease in pulmonary artery pressure at rest and during exercise; treatment with nifedipine for 4 months produced substantial clinical benefits associated with persistent favorable effects on cardiac output but less marked effects on pulmonary artery pressure. Beneficial short-term hemodynamic responses to verapamil and diltiazem have also been reported,[57,58] and long-term treatment in some of these cases was followed by clinical improvement. Unfortunately, all of these reports are isolated case studies; we do not know how representative these findings are because each concerned an individual patient. Furthermore, the relation between any observed benefit and treatment with a calcium-channel antagonist is unclear, because in none of these cases was treatment withdrawn in order to determine whether benefits were directly related to the drug. This is important, because spontaneous hemodynamic improvement in patients with primary pulmonary hypertension may not be uncommon.[59,60]

Further experience in larger series of patients has generally supported the benefits of calcium-channel blockade. Rubin et al[61] evaluated 9 patients with primary pulmonary hypertension who were treated with nifedipine, 10 to 20 mg sublingually initially, followed by oral therapy with 40 to 160 mg daily for 4 to 14 months in 6 patients. Short-term treatment with nifedipine produced marked increases in cardiac output and decreases in total pulmonary resistance with notable decreases in pulmonary artery pressure in many patients. These favorable responses were associated with a significant decrease in right ventricular end-systolic and end-diastolic volumes and an increase in right ventricular ejection fraction as determined by radionuclide angiography, the magnitude of which correlated with the decrease in total pulmonary resistance. Long-term therapy produced persistent hemodynamic benefits associated with improvement in symptoms. Similar responses were seen by Olivari et al[62] in 7 patients with primary pulmonary hypertension. In this study, nifedipine, 20 mg sublingually, increased cardiac output and decreased pulmonary artery pressure and pulmonary vascular resistance at rest; these benefits were also observed in 3 patients during exercise. Unfortunately, no long-term results were reported. Mc Leon et al[63] noted similar immediate effects in 4 patients given 20 mg of nifedipine sublingually. Hemodynamic improvement was sustained after 4 months in the 2 patients who were invasively reevaluated while receiving a daily dose of 40 mg daily; total work capacity increased markedly.

However, adverse effects during calcium-channel blockade have been reported with increasing frequency as experience with these drugs has increased. Rubin et al[61] reported that a patient who failed to have a pulmonary vasodilator response with nifedipine had a marked increase in pulmonary artery pressure as cardiac output and heart rate increased consequent to

systemic vasodilation. This was probably the result of reflex activation of the sympathetic nervous system and is similar to the occasional exacerbations of pulmonary hypertension seen after administration of isoproterenol to patients with primary pulmonary hypertension.[13,48] Similarly, although nifedipine produced significant pulmonary vasodilation in the patients reported by Summer et al,[64] severe adverse reactions (hypotension and gastrointestinal distress) were seen in each of the 5 patients they treated. Even more serious adverse effects were seen in 9 patients with primary pulmonary hypertension treated with verapamil by Landmark et al.[57] Verapamil infused directly into the pulmonary artery produced marked decreases in pulmonary artery pressure but little change in cardiac output or pulmonary vascular resistance. In 3 patients, however, a marked decrease in cardiac index was observed; this was associated with dyspnea and hypotension in 1. These unfavorable responses to verapamil were attributed to its negative inotropic effects[15]; that similar deleterious effects were not reported with nifedipine was attributed to its less marked cardiodepressant action.[52]

Preliminary results from our laboratory, however, indicate that marked depressant effects on right ventricular function may accompany the use of both nifedipine and verapamil in patients with primary pulmonary hypertension. In 7 such patients who we treated with oral and intravenous verapamil[65] and in 6 patients treated with oral nifedipine,[66] pulmonary vascular resistance was decreased significantly in a fashion similar to the reports of other investigators. However, cardiac index failed to increase with either drug, despite the decrease in impedance to right ventricular ejection that would normally be expected to improve cardiac performance. This unexpected response was a consequence of a marked deterioration in right ventricular performance during treatment with both calcium antagonists, as reflected by a substantial decrease in mean pulmonary artery pressure (and, hence transpulmonary driving pressure) and a marked increase in right ventricular filling pressure. These deleterious responses differed markedly from those seen with hydralazine, which increased cardiac output in these same patients without significant effects on mean pulmonary arterial pressure or mean right atrial pressure. These unfavorable effects of verapamil and nifedipine were accompanied by severe adverse clinical events, including the precipitation of severe hypotension and cardiogenic shock during short-term therapy in 2 patients and the exacerbation of right-side heart failure during long-term treatment in 3 patients.

The detrimental effects we observed with calcium-channel blockade in our patients with primary pulmonary hypertension are in marked contrast to the favorable effects on right ventricular function reported by Rubin et al[61] and the resolution of clinical right-side heart failure during long-term therapy reported by Camerini et al.[53] The reasons underlying such differences are unclear, but they may be related to the severity of right ventricular dysfunction in our patients, all of whom had a right ventricular ejection fraction <30% and most of whom had a mean right atrial pressure >10 mm Hg. Right ventricular filling pressure was not generally measured in previous reports on the use of nifedipine in pulmonary hypertension, and only 1 group of investigators measured the right ventricular ejection fraction before therapy.[61] If the severity of right ventricular dysfunction in our patients were greater than in previous reports, it might explain the detrimental responses we observed, because the cardiodepressant effects of calcium-channel blockade are largely determined by the severity of preexisting ventricular dysfunction.[67] In patients with severe left ventricular dysfunction, both verapamil and nifedipine can exacerbate left-side heart failure.[67,68] Our results indicate that in patients with preexisting severe right ventricular dysfunction, both drugs can aggravate right-side heart failure as well, regardless of whether the cause is primary[65,66] or secondary[63] pulmonary hypertension. These cardiodepressant effects are consistent with the ability of both drugs to block transmembrane calcium in cardiac muscle and thus depress myocardial contractility.[15,69]

In summary, although calcium-channel antagonism provides a logical approach to the treatment of a variety of pulmonary hypertensive states, the beneficial responses to these drugs, have largely been observed only during short-term administration to well-compensated, carefully selected patients treated under close supervision. The long-term effectiveness and safety of this therapeutic approach remains to be established, particularly in view of the deleterious effects on right ventricular function that may accompany treatment with these drugs in patients with severely advanced disease. Calcium-channel blockade might prove useful in the treatment of patients with early or mild pulmonary hypertension (or both), because the pulmonary vasculature in such patients may still be responsive to vasodilator stimuli and their right ventricular performance may be less likely to be adversely affected by the negative inotropic effects of these potent cardioactive drugs.

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Calcium-Channel Blockers in Prophylaxis and Treatment of Asthma

CHRISTOPHER H. FANTA, MD

Calcium-channel blocking drugs do not induce bronchoconstriction in susceptible persons with cardiac disease and concomitant hyperreactive airways (such as asthma or chronic bronchitis). The ways in which calcium blockers might in fact play a beneficial role in preventing bronchoconstriction or inducing bronchodilation in asthma are explored. Nifedipine and verapamil have been shown to inhibit the bronchoconstriction provoked by exercise, histamine, methacholine and antigen. The potential mechanisms by which this protective effect is mediated—whether by direct action on tracheobronchial smooth muscle, inhibition of release of mediators from activated mast cells or both—are examined by reviewing in vitro studies of both cell systems. Calcium blockers also exhibit some bronchodilating activity in vitro. Early clinical trials of these drugs in ambulatory asthmatic patients have shown little, if any, therapeutic benefit, but results must be considered preliminary in view of the nature of the short-term, small-scale trials performed to date. Regardless of their therapeutic potential in obstructive lung diseases, the calcium-channel blockers offer a powerful probe into the role of calcium in the physiologic make-up of airways and, in particular, the pathophysiologic features of airway hyperreactivity.

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In the past, the physician treating a patient with both angina and asthma was faced with a difficult dilemma. The most potent antianginal medications available, the β-adrenergic blockers, were contraindicated in the presence of asthma, and the β-adrenergic stimulants frequently used to treat asthma were likely to exacerbate the angina. Now, with the introduction of calcium-channel blockers, a new class of drugs is available to treat angina and other cardiac diseases that has the potential for application in the subpopulation of patients with concomitant airway obstruction.

To the cardiologist, then, the airway effects of the calcium-channel blockers are important because of the lack of bronchoconstriction induced by these drugs. Unlike β-blockers, calcium-channel blockers do not exacerbate airway obstruction in susceptible persons.[1–3] In 1967, Atterhög reported that intravenous verapamil administered for control of cardiac arrhythmia caused no worsening of lung function in 3 patients with concomitant asthma. Subsequently, Ringqvist[2] administered 10 mg of verapamil intravenously to 9 subjects with moderately severe chronic obstructive lung disease and found no increase in their mean lung resistance. More recently, among a group of 18 patients with angina and either chronic bronchitis or asthma, Jaiprakash et al[3] found no deterioration in lung mechanics (1-second forced expiratory volume [FEV_1], vital capacity or airway resistance) during a 2-week period of treatment with nifedipine, 10 mg orally, three times daily. According to these studies, this new class of cardioactive agents is safe for use in patients with concomitant obstructive lung disease, including asthma.

To the pulmonologist, on the other hand, the attraction of the calcium-channel blockers is their potential for beneficial airway effects; that is, for inhibiting bronchoconstriction and inducing bronchodilation in reactive airway diseases. It is tempting to conceive of asthma as analogous to Prinzmetal's angina:[4] both bronchospasm and coronary vasospasm are exaggerated contractile responses of smooth muscle tissue. The contractile machinery of airway smooth muscle, as of coronary artery smooth muscle, is calcium-dependent and is regulated, at least in part, by the transmembrane influx of calcium ions.[5,6] The spectacular efficacy of calcium-channel blockers in treating Prinzmetal's angina[7] encourages the pulmonologist to explore the effect of calcium-channel blockade in bronchospastic disorders.

From the Brigham and Women's Hospital, Boston, Massachusetts. This study was supported in part by the Edward Livingston Trudeau Scholar Award of the American Lung Association and by Grant HL 16463 from the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland.

Address for reprints: Christopher H. Fanta, MD, Pulmonary Diseases Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115.

TABLE I Calcium-Channel Blockers in Exercise-Induced Bronchoconstriction (Additional Studies)

Report	Drug (Dose and Route)	Subjects (n)	Postexercise Decrease in Expiratory Flow (%)*		Significance (p Value)
			Placebo	Drug	
Patel[16]	Verapamil (approximately 3 mg inhaled)	10	45 ± 4	17 ± 4	<0.01
Patel[17]	Nifedipine (20 mg sublingually)	15	32 ± 4	22 ± 4	<0.01
Barnes et al[18]	Nifedipine (20 mg sublingually)	8	57 ± 4	36 ± 5	<0.01
Corris et al[19]	Nifedipine (20 mg sublingually)	8	24 ± 4	6 ± 5	<0.001

* Mean ± standard error of the mean.

In fact, multiple pathways in the pathogenesis of asthma are influenced by intracellular calcium ion concentrations and might be susceptible to manipulation by inhibitors of calcium ion influx.[8–10] Not only constriction of tracheobronchial smooth muscle but also mast cell degranulation, mucous gland secretion and vagal neurotransmission are mechanisms for airflow obstruction that may be modulated by the calcium ion. Of these latter 3 pathways, the role of calcium in mediator release from mast cells has been the most extensively studied. Extracellular calcium must be available for antigen-induced release of histamine from sensitized mast cells to proceed.[11] After antigen-antibody interaction on the cell surface (or stimulation with ionophores), altered membrane permeability occurs, which allows calcium to enter the cell; mediator release follows in direct proportion to calcium influx.[12] The ability to prevent calcium from entering into these cells might uncouple the antigen-antibody stimulus from the secretory response. The calcium-channel blockers have been found to interfere with secretory processes in other tissues, such as pancreas[13] and pituitary gland.[14] Their inhibition of release of the mediators of immediate hypersensitivity from mast cells could provide an important therapeutic intervention in asthma.

Prophylaxis of Exercise-Induced Bronchoconstriction

To explore the potential role of calcium-channel blockers in the prevention of bronchoconstriction, Cerrina et al[15] administered 20 mg of nifedipine sublingually to 10 asthmatic patients before exercise. Each subject performed 10 minutes of steady-state exercise on a bicycle ergometer on 3 separate occasions: once on a control day without any premedication, and then again on 2 additional days 30 minutes after premedication with either placebo or nifedipine in a single-blind fashion. Airflow obstruction was assessed by measuring peak expiratory flow rate (PEFR) and flow after exhalation of 50 and 75% of the vital capacity ($\dot{V}max_{50}$ and $\dot{V}max_{25}$). All 3 parameters demonstrated a mean decrease of approximately 40% from baseline values after exercise on the control and the placebo premedication days, but no deviation from the normal range when exercise was preceded by nifedipine administration (Fig. 1). These investigators found that nifedipine completely protected asthmatic subjects from exercise-induced bronchoconstriction. At the same time, they found that sublingual nifedipine (20 mg) failed to alter resting lung function in another group of 10 asthmatic patients.[15]

Subsequent to this dramatic initial report, 4 studies have confirmed a beneficial effect of the calcium-channel blockers in exercise-induced bronchoconstriction, but the protection observed has been more modest.[16–19] The results of these studies are summarized in Table I. Bronchoconstriction was significantly inhibited by premedication with either sublingual nifedipine or inhaled verapamil; but, as the mean postexercise values for expiratory flow indicate, protection was only partial. In each study the investigators reported considerable intersubject variability: a few subjects had complete inhibition of bronchoconstriction, a few had no inhibition and most had partial inhibition by a calcium-channel blocker.

Cromolyn is widely used clinically as prophylactic therapy in exercise-induced asthma.[20] Patel[17] compared the effect of inhaled verapamil (approximately 3 mg) with inhaled cromolyn (approximately 12 mg by nebulized solution) in exercise-induced bronchoconstriction and found virtually identical protection.

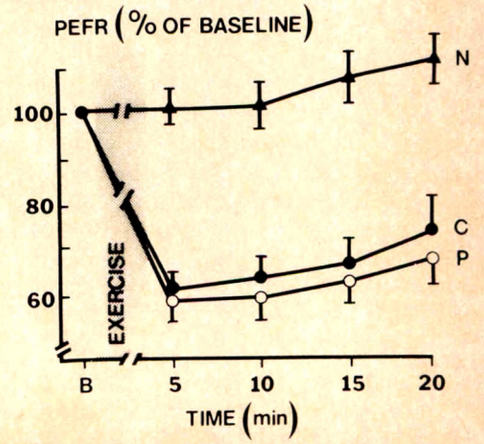

FIGURE 1. Inhibition of exercise-induced bronchoconstriction by sublingual nifedipine. C = control, N = nifedipine; P = placebo, PEFR = peak expiratory flow rate. **Hatched bar** represents 10 mintues of steady-state bicycle exercise. Each point is the mean of 10 subjects; parallel lines enclose 1 standard deviation. (Adapted from Cerrina et al.[15])

Prophylaxis of Inhalational Challenges: Histamine, Methacholine and Antigen

Because the role of mediator release in the pathogenesis of exercise-induced bronchoconstriction remains controversial,[21,22] the finding that calcium blockers have a protective effect in this setting does not help to localize their site of action. As illustrated schematically in Figure 2, calcium-channel blockers may exert their inhibition by blocking mast cell degranulation, by directly interfering with bronchial smooth muscle contraction or by both mechanisms. One approach to this question is to assess the effect of these agents on bronchoconstriction triggered by stimuli other than exercise, where the pathways for constriction are better defined. Examples of such stimuli include histamine, which is thought to induce bronchoconstriction through both reflex (vagal) pathways and direct stimulation of smooth muscle receptors; methacholine, which acts like a cholinergic neurotransmitter to stimulate smooth muscle constriction directly; and antigens, which of course trigger mast cell secretion. In recent years, a number of reports have emerged examining the effect of calcium-channel blockers in these various circumstances, both in man and in animal models. The results of these studies, which are reviewed herein, are not entirely consistent. On the whole, however, they do provide evidence for a direct action of the calcium-channel blockers on tracheobronchial smooth muscle.

Histamine and methacholine inhalational tests in asthmatic patients: Four studies of asthmatic patients have found that sublingual nifedipine decreases the bronchoconstrictive response to inhaled histamine.[18,19,23,24] In 3 reports (from 2 different laboratories)[18,19,23] the concentration of histamine provoking a 20% decrease in FEV_1 (PC_{20}) was calculated by administering incremental concentrations of inhaled histamine in dose-response fashion. The mean PC_{20} for histamine after premedication with nifedipine was approximately 2 to 3-fold greater compared with placebo pretreatment. In the fourth study,[24] the mean fall in FEV_1 after a fixed concentration of inhaled histamine was 32 ± 15% (standard error of the mean) after placebo versus 22 ± 12% after nifedipine ($p < 0.01$). In 1 study reporting no protective action of sublingual nifedipine,[25] there was a wide range of bronchial reactivity among subjects; mean values showed a nonsignificant trend toward a higher PC_{20} for histamine after nifedipine, and in 4 of 8 subjects the PC_{20} was 2 or more times greater after nifedipine compared with placebo.

Similarly, nifedipine has been shown to blunt the bronchospastic response to inhaled methacholine, both in asthmatic patients[24] and in patients with coronary artery disease but without airway hyperreactivity.[26] These reports suggest an action of the calcium-channel blocking drugs independent of any mast cell effects, probably an action at the level of airway smooth muscle itself.

The protective benefit afforded in these bronchoprovocative challenges is, however, quite modest. Direct comparisons with frequently used bronchodilating drugs are few. In 1 investigation of 15 asthmatic patients,[27] repetitive histamine dose-response inhalation tests were performed on a single day with premedication randomized to saline solution, verapamil and salbutamol; all 3 were administered by nebulizer. Approximately 2.5 mg of verapamil and 1.0 mg of salbutamol were nebulized; more precise estimates of inhaled or retained doses were not made. Verapamil increased the PC_{20} for histamine 1.8-fold (not a significant increment when compared with saline solution), whereas salbutamol caused a 16.8-fold increase. Others have also found that inhaled sympathomimetics, in delivered doses as low as 200 μg, increase the PC_{20} for histamine or methacholine 10-fold or more.[28,29] One must be cautious, however, in extrapolating these laboratory data using bronchoprovocative agonists to clinical therapeutics. For example, the *oral* administration of bronchodilating drugs such as salbutamol or a theophylline preparation before histamine or methacholine challenge alters responsiveness by a factor of only 2 to 3.[28,29] Based on this limited protection, one would not predict their widespread clinical utility.

In vitro studies of tracheobronchial smooth muscle: In vitro experiments using human bronchial spirals[30,31] and tracheal strips[32] have lent support to the

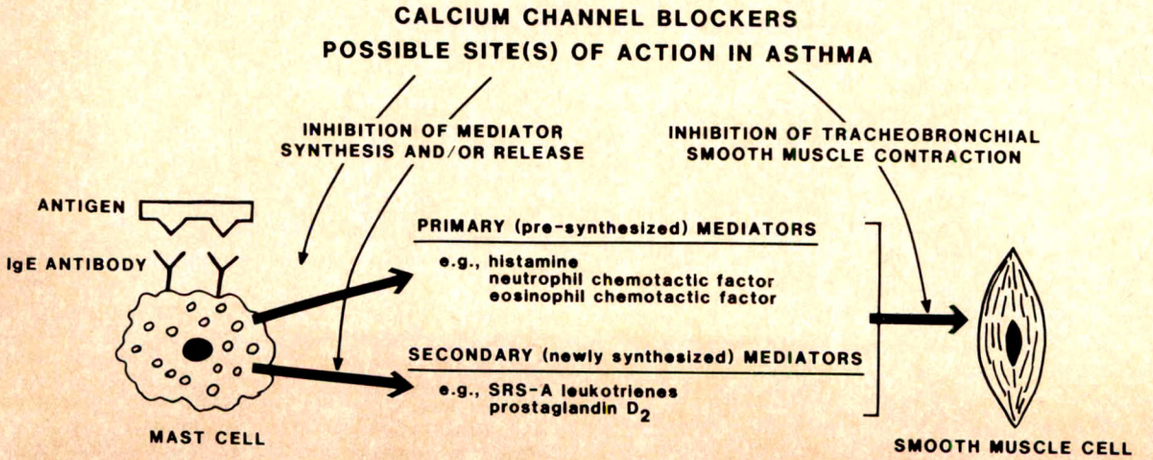

FIGURE 2. Schematic representation of mast cell, mediators of immediate hypersensitivity and target tracheobronchial smooth muscle cell, indicating possible sites of action of calcium-channel blockers.

theory that calcium-channel blockers directly inhibit contraction of tracheobronchial smooth muscle, which is the final common pathway for acute bronchospasm. Drazen et al[32] prepared strips of trachealis muscle from autopsy material, generally obtained within 8 hours after death. These strips were suspended in glass organ baths, bathed with a physiologic solution and gassed with 95% oxygen and 5% carbon dioxide. One end of each strip was fixed to a transducer for recording of contractile force. This tracheal tissue was shown to constrict in dose-response fashion to incremental concentrations of histamine added to the organ bath. Two reproducible concentration-effect curves could be generated in succession. When nifedipine (3 μM) was incubated with the tissue strips for 10 minutes before a second concentration-effect sequence was performed, contraction of the trachealis muscle was significantly inhibited (Fig. 3). At the highest histamine concentration (100 μM), nifedipine inhibited constriction by 50 ± 2%. Verapamil has likewise been shown to inhibit histamine-induced constriction of human bronchial strips.[31]

This inhibitory effect is not limited to a specific antagonism of histamine. Studies with human bronchial smooth muscle have demonstrated inhibition of acetylcholine-induced constriction as well,[30] and animal studies using guinea pig and canine airway tissue strips have extended the spectrum of bronchoconstrictor agonists inhibited by calcium blockers to include potassium, carbachol, serotonin, prostaglandin $F_{2\alpha}$ and leukotriene D_4.[5,33–37] Thus, specific antihistaminic or anticholinergic properties of calcium blockers cannot account for their observed effects. That calcium blockers' mechanism of action is based on their influencing calcium availability for the cytostolic contractile apparatus is supported by the observation that their inhibitory effect on tracheobronchial smooth muscle contraction can be overcome by increasing the extracellular calcium concentration.[35] This has also been demonstrated for coronary vascular smooth muscle.[38]

Inhibitory activity of calcium blockers is not limited to central airway tissue, as represented by tracheal spirals. The same inhibition of constriction has been demonstated using lung parenchymal strips,[35] which contain contractile elements from peripheral airways.

The duration of protection against pharmacologically induced bronchoconstriction afforded by the calcium-channel blockers has been examined in a canine model.[39] After a single intravenous injection of 200 μg/kg of nifedipine in anesthetized beagles, protection was observed within 15 minutes, reached a maximum at 60 to 90 minutes and persisted against repetitive histamine challenges for up to 240 minutes.[39] In these dogs, a delivered dose of aerosolized nifedipine of only 140 μg also protected against histamine-induced increases in pulmonary resistance, but the duration of action by this route was briefer (60 minutes).[39]

Sources of calcium for tracheobronchial smooth muscle contraction: From the studies cited previously, it would seem reasonable to conclude that calcium flow into tracheobronchial smooth muscle can be stimulated by a variety of bronchoconstrictor agonists; that by blocking this calcium ion influx the calcium-channel blockers can inhibit bronchoconstriction; and that inhibition of histamine- and methacholine-induced constriction in man can be achieved by this mechanism of action after administration of standard drug doses. Yet some questions remain. Why don't calcium-channel blockers provide more complete protection against bronchoconstriction? Why does submaximal airway constriction still take place, even in the presence of relatively high concentrations of channel blockers in vitro? One possible explanation invokes differential tissue sensitivites to drug activity between airways and other clinically more responsive tissues, such as the coronary vasculature. However, when potassium-induced contractions of coronary artery and trachea are compared in vitro, nifedipine exhibits virtually identical concentration-dependent inhibitory activity in the 2 tissues, as shown in Figure 4,[40] (even though this comparison is between 2 different animal species).

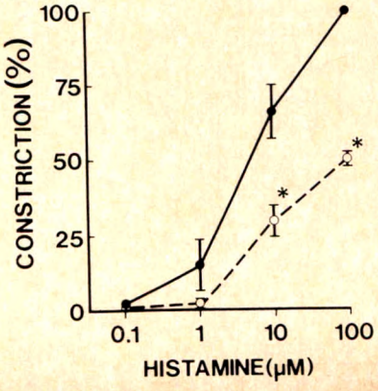

FIGURE 3. Inhibition of constriction of human tracheal strips in vitro. **Closed circles** and **solid lines** represent control tissues; **open circles** and **dashed lines** represent tissues preincubated with nifedipine, 3 μM. Each point is the mean of 6 tissues; parallel lines enclose 1 standard error of the mean. Reprinted with permission from Fanta.[77]

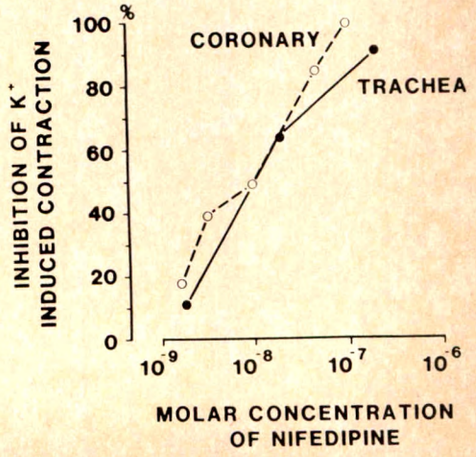

FIGURE 4. Comparison of inhibition of contraction of pig coronary artery strips and guinea pig tracheal strips in vitro. Coronary tissue was constricted with 43 mM extracellular potassium; nifedipine was then added to organ bath in increasing concentrations.[40] Tracheal strips were preincubated with varying concentrations of nifedipine before constriction with 60 mM potassium (unpublished observations).

Rather, the explanation may be that pharmacologically induced constriction of tracheobronchial smooth muscle makes calcium available to the contractile apparatus through routes other than those acted upon by calcium-channel blockers.[41] The following observations support this contention. Increased levels of extracellular potassium depolarize trachealis muscle; contractile tension develops in direct proportion to membrane depolarization ("electromechanical coupling"), and this contraction is virtually entirely dependent on calcium influx from the extracellular fluid.[42,44] In relatively low doses, the calcium-channel blockers completely abolish potassium-induced contraction of tracheal smooth muscle.[5,37,45,46] On the other hand, pharmacologic bronchoconstrictors such as histamine, acetylcholine and serotonin cause tracheal contraction that is in large part independent of membrane depolarization, especially at higher drug concentrations.[6,42,44] This "pharmacomechanical coupling" is less dependent on the influx of extracellular calcium than is potassium-induced contraction,[6,45] although the intracellular pools of calcium presumed to be activated by the constrictor drugs do become depleted over time if extracellular calcium is not made available to replenish them.[6,42,45,47] Calcium-channel entry blockers only partially inhibit mediator-induced constriction; they are less active by 100-fold or more as inhibitors of contraction caused by leukotriene D_4,[47] histamine[37,46] or acetylcholine[37,48] than they are against potassium-induced contraction. Thus, even in the presence of calcium-channel entry blockers, pharmacologic agents can initiate receptor-mediated events that make calcium available to the contractile apparatus. This mechanism probably involves intracellular sources of calcium as well as transmembrane calcium flux unimpeded by calcium blockers, similar to the "receptor-operated channels" described for vascular and other smooth muscle.[49] Thus, it is not surprising to find incomplete protection from histamine or methacholine-induced bronchospasm in asthmatic patients pretreated with presently available calcium-channel blocking drugs.

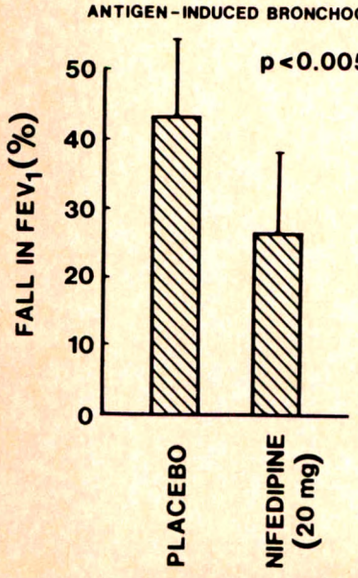

FIGURE 5. Inhibition of antigen-induced bronchoconstriction by nifedipine. Fall in FEV_1 equals decrease in 1-second forced expiratory volume from before to after antigen challenge. The mean and 1 standard error of the mean are shown for 8 subjects. (Adapted from Henderson et al.[30])

Antigen inhalation challenges in asthmatic patients: Inhalation of antigen in the allergic asthmatic patient triggers a complex series of events: over the short term, antigen binds to IgE antibodies on the surface of mast cells; "bridging" between adjacent IgE molecules triggers alterations in the cellular plasma membrane; calcium enters the cell and there follows the release of presynthesized mediators of immediate hypersensitivity, such as histamine, as well as the generation and release of newly synthesized mediators, such as slow-reacting substance of anaphylaxis (SRS-A).[50] Besides this acute or "early-phase" reaction inhaled allergens may also form circulating antigen-antibody complexes, leading to delayed or "late-phase" inflammatory reactions.[51]

Sublingual nifedipine has been shown to inhibit the acute bronchospastic response to inhaled allergen in asthmatic patients. Henderson et al[30] administered nifedipine, 20 mg, or placebo in double-blind fashion to 8 grass-pollen–sensitive asthmatic patients 30 minutes before challenge with inhaled grass-pollen antigen. A single dose of antigen was given on both drug and placebo days; the dose was selected on a previous day and was sufficient to cause at least a 25% decrease in FEV_1. Data from this study are shown in Figure 5. The mean decrease in FEV_1 in response to inhaled antigen was 43 ± 10% after placebo pretreatment and 27 ± 12% after nifedipine ($p < 0.005$). The degree of protection afforded by the calcium-channel blocker varied considerably from subject to subject: in 3 of the 8 subjects the percent decrease in FEV_1 with nifedipine was less than half that with placebo.[30]

Two other groups of investigators were unable to demonstrate altered responsiveness to antigen challenge by premedication with a calcium-channel blocker.[52,53] These discordant results may be explained in part by use of a different calcium blocker (verapamil) through a different route of administration (inhalation).[52,53] In 1 of these studies with negative results, sublingual nifedipine was also tested[52]: the provocative dose of allergen required to cause a 20% decrease in FEV_1 (PD_{20}) was the outcome variable measured. Because of the day-to-day variability in antigen-provocation testing, a 10-fold increase in PD_{20} was considered necessary to demonstrate a significant change from placebo. This degree of protection was not provided by the single dose of nifedipine.

Animal studies have confirmed that calcium-channel blockers can modify the airway response to inhaled antigen.[54,56] In Basenji greyhound dogs, a model of spontaneously occurring nonspecific airway hyperreactivity, aerosolized nifedipine (12.5 mg delivered dose) significantly reduced the increase in pulmonary resistance and the decrease in dynamic compliance caused by inhalation of Ascaris suum antigen.[54] The 40% ethanol solution in which nifedipine was dissolved

had no effect on lung function in control studies. Nifedipine aerosol also blunted the bronchoconstrictive response to inhaled methacholine and citric acid in these dogs.[54] On the other hand, although completely blocking antigen-induced bronchoconstriction in Ascaris-sensitive sheep, intravenous verapamil (150 μg/kg) had no influence on histamine or carbachol inhalation challenges in these animals.[55] These latter findings at least raise the possibility that, in sheep, parenteral verapamil exerted its protective effect by preventing mast cell activation in the absence of significant direct bronchial smooth muscle effects.[55]

In vitro studies of mediator release: The effect of calcium-channel blockers on mast cell activity has been investigated in vitro. Using rat peritoneal mast cells, it has been possible to demonstrate that the transmembrane influx of calcium initiated by antigen-IgE antibody binding can indeed be inhibited by preincubating the mast cells with a calcium blocker (in this case, nifedipine).[57] However, the impact of this calcium-entry blockade on mediator release is not straightforward.

Nifedipine blunts ionophore-induced release of histamine from human basophils.[58] In contrast, when antigen-induced release of histamine was analyzed using leukocyte suspensions from patients with hay fever,[59] passively sensitized fragments of human lung tissue[31] or an anaphylactic model of guinea pig trachea,[37] high concentrations of nifedipine or verapamil failed to modify antigen-stimulated histamine release. On the other hand, when SRS-A is the mast cell product assayed, decreased amounts are found when lung fragments[31,60] or peripheral blood neutrophils[61] are stimulated after preincubation with a calcium-channel blocker. Unlike histamine, SRS-A, which is now known to be a mixture of the leukotrienes C_4, D_4 and E_4, is synthesized de novo from arachidonic acid at the time of antigen stimulation.[50] The enzyme phospholipase A_2, which liberates arachidonic acid from membrane phospholipids, and the 5-lipoxygenase enzyme system, which initiates the conversion of arachidonic acid to the leukotriene metabolic pathway, are both calcium-dependent.[63,64] Calcium depletion will thus inhibit SRS-A leukotriene formation as well as release.[65] It may be, then, that by reducing transmembrane calcium ion flux into mast cells, calcium-channel blockers may inhibit leukotriene synthesis while not affecting secretion of the prepackaged histamine-containing granules.[66] This suppression of leukotriene release, although permitting histamine release to proceed unattenuated, has been described in a number of other circumstances, such as challenge with antigen in the presence of cytochalasins or certain concentration ratios of sympatho- and parasympathomimetics.[50]

A combination of cromolyn and a calcium-channel blocker in the prophylaxis of antigen-induced bronchoconstriction has not been reported, nor has the effect of calcium blockers on the "late-phase" of airway obstruction after antigen challenge been investigated.

Bronchodilating Action of Calcium-Channel Blockers

On the basis of these laboratory data regarding the prophylaxis of induced bronchoconstriction, it would be difficult to predict the role of calcium-channel blockers in routine outpatient management of patients with symptomatic asthma. Uniformly, investigators have found no bronchodilating effect of single doses of nifedipine or verapamil when given to subjects with mild, asymptomatic asthma recruited for bronchoprovocation testing.[15–19,23–25,27,30,52,53] However, in vitro studies would suggest that calcium-channel blockers can indeed exert a bronchodilating action.

Only a small, usually insignificant relaxant effect has been observed when calcium blockers were incubated

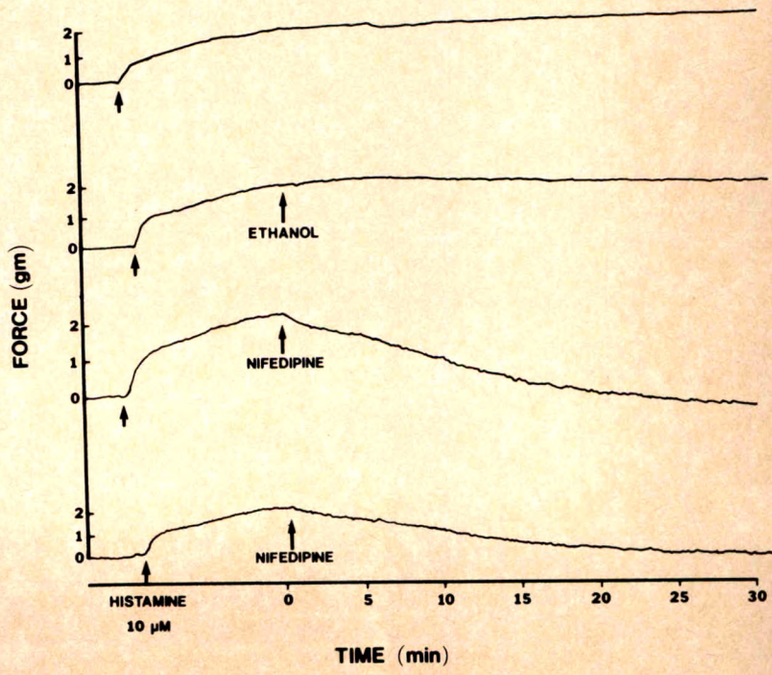

FIGURE 6. Nifedipine-induced relaxation of human tracheal strips in vitro. Actual strip chart recordings for 4 human tracheal strips are shown. Each was initially constricted by incubation with 10 μM of histamine. To **top strip,** nothing was added; to **second strip,** 0.1% ethanol (diluent for nifedipine); to **third** and **bottom strips,** nifedipine, 3 μM. Reprinted with permission from Drazen et al.[32]

with tracheal or lung parenchymal strips held at resting levels of tension.[30,32,35,47] This observation is somewhat surprising, given the finding that exposure to a calcium-free bath causes marked relaxation of resting tone in guinea pig trachea.[67] On the other hand, calcium-channel blockers will cause relaxation of guinea pig and human tracheal strips previously constricted by various pharmacologic agonists or by anaphylaxis[32,37,68–70] (Fig. 6). This bronchodilating action may vary depending on the agent used to promote bronchoconstriction: Weichman et al[47] found that nifedipine showed only a weak ability to relax leukotriene D_4-induced contraction of trachealis muscle while completely reversing contraction elicited by potassium. Differences in bronchodilating potency among the calcium-channel blockers probably also exist, with nifedipine having greater activity than verapamil or diltiazem.[47,71]

Using guinea pig tracheal tissue as an in vitro assay, the bronchodilating activity of calcium-channel blockers was compared with other bronchodilating agents. The concentration of diltiazem causing 50% relaxation of a maximum histamine-induced contraction (approximately 10^{-4} M diltiazem) is of the same order as that of theophylline[37,72] but is 1,000 or more times greater than for isoproterenol.[68,72] In an in situ preparation of canine trachea, intraarterial injection of nifedipine, 10 μg, produced less tracheal dilation than 0.1 μg of isoproterenol.[71] The mechanisms by which isoproterenol and calcium blockers achieve airway smooth muscle relaxation differ: the former is inhibited by propranolol, the latter appear not to be.[68] There exists the potential, therefore, of synergistic effects when the 2 classes of drugs are used in combination. In vitro evidence for such potentiation of bronchodilation by calcium-channel blockers has been contradictory to date.[33,68] However, enhancement of the bronchodilating effect of isoproterenol[68] and theophylline[73] by calcium blockers has been reported for guinea pig airway tissue in vitro.

Treatment Trials in Asthma

Adequate clinical trials of the calcium-channel blockers in patients with symptomatic asthma are lacking. One double-blind, placebo-controlled, crossover trial of oral verapamil was conducted in 10 asthmatic patients in 1970.[74] No change in FEV_1 or vital capacity, measured weekly, was observed during verapamil treatment as compared with placebo. However, the dosage of drug used, 40 mg 3 times daily, is now recognized to be far below the range at which maximal therapeutic effects are likely to be seen.[40] More recently, a group of 11 asthmatic patients was given nifedipine, 10 mg orally 3 times daily, or placebo for 4 days each in a randomized, double-blind, crossover protocol.[75] In these patients, all of whom had significant bronchoconstriction at rest (mean FEV_1 51%), a single oral dose of nifedipine, 10 mg, caused significant bronchodilation; the mean increase in FEV_1 2 hours after ingestion was 18% (versus 4% after placebo; $p < 0.05$). Eight of the 11 patients used an inhaled sympathomimetic throughout the protocol period. Patients self-recorded their PEFRs using Wright peak flowmeters at home. No differences were found between nifedipine and placebo treatment periods with respect to morning or evening PEFR determinations. The investigators reported that the nocturnal decrease in PEFR, a feature of the disease in all 11 patients, was decreased by a statistically significant amount during nifedipine treatment. However, because symptom scores recorded each morning by the subjects did not differ from 1 treatment period to the other, the clinical importance of this observation is dubious. Without question, additional clinical studies are needed to evaluate more fully the bronchodilator potential of the calcium-channel blockers, both alone and in combination with traditional bronchodilators. The available evidence does not indicate that the calcium-channel blockers currently in use are potent bronchodilators. However, as stated by Weiss et al,[37] the potential remains that eventually "control of calcium dynamics may offer innovative therapeutic modalities in the management of bronchial asthma."

Finally, it has been suggested[4,41,76] that disordered calcium metabolism may prove to be the basis for the underlying airway hyperreactivity that characterizes asthma. For the most part, this concept is pure speculation. The observation of Weiss and Viswanath[67] that after anaphylaxis, guinea pig trachealis muscle exhibits a heightened sensitivity to extracellular calcium may be pertinent. Calcium-channel blockers may help to elucidate abnormalities of calcium entry into cells or exaggerated contractile responses to intracellular calcium ion concentrations in patients with asthma.

In summary, calcium-channel blocking drugs are an important contribution to the therapy of patients with angina and concomitant reactive airway disease because they do not exacerbate airflow obstruction in such susceptible persons. Furthermore, they act to inhibit bronchoconstriction induced in asthmatic patients by a variety of stimuli, including exercise, histamine, methacholine and allergens, although in general their protection is limited. They appear to exert their effect by a direct inhibitory action on contraction of tracheobronchial smooth muscle. Inhibition of antigen-induced histamine release from human mast cells has not been demonstrated. However, calcium-channel blockers may interfere with the synthesis or release of leukotrienes from lung tissue, and some of their protective role in the prevention of bronchoconstriction may be through this mechanism of action. Adequate clinical trials of calcium-channel blockers in patients with asthma and other obstructive lung diseases are needed. Presently available evidence does not point to a major bronchodilator role for these drugs; they do serve, however, as a powerful probe into the role of calcium in airway physiology and in the pathophysiologic features of asthma.[77]

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Calcium-Channel Blocking Agents for Gastrointestinal Disorders

DONALD O. CASTELL, MD

Calcium-channel blocking agents have a potential role in regulation of gastrointestinal tract function by decreasing smooth muscle contraction and possibly inhibiting cellular secretion. Most studies to date have concentrated on the ability of these drugs to inhibit smooth muscle contraction. Verapamil and diltiazem have been shown in animals (opossum, baboon) to produce decreased contractions in esophageal smooth muscle, resulting in a decreased amplitude of peristalsis and decreased lower esophageal sphincter pressures. In studies in man, oral doses of diltiazem and nifedipine have likewise been shown to have similar effects on the esophagus. At present, there is no experimental evidence of a major antisecretory effect of these drugs. In clinical trials, nifedipine has been shown to have a greater effect than placebo in improving symptoms in patients with achalasia, and diltiazem has been suggested as potential therapy in patients with chest pain secondary to excessive esophageal contraction. The precise role for calcium-channel blocking drugs in therapy of gastrointestinal disease is still being explored.

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The calcium-channel blocking drugs verapamil, nifedipine and diltiazem relax smooth muscles by inhibiting membrane fluxes of calcium into the cells. The active inhibitory effects demonstrated by these agents on vascular smooth muscle raise the question of the potential for similar effects on smooth muscle of the gastrointestinal tract.[1] In addition, the secretory functions in the gastrointestinal glands have all been shown to be dependent to some degree on intracellular calcium shifts. Thus, effects on gastric acid, pancreatic enzyme and bicarbonate secretion and even intestinal fluid output might conceivably be modified by drugs that inhibit calcium entry.

Pharmacologic Studies in Animals

Pharmacologic studies to date have primarily addressed the effects of calcium-entry blocking agents on contraction patterns in the smooth muscles of the gastrointestinal tract. Further, most studies have looked at the action of these drugs on the smooth muscle portion of the esophagus, primarily because of the greater ease of studying the contraction patterns of this area of the gastrointestinal tract (Table I). The opossum has been a popular animal model for studies of esophageal function because of its size and the similarity of its esophageal muscular structure to that of humans. Studies of verapamil (64 μg/kg/min) in opossum reveal a gradual decrease in lower esophageal sphincter (LES) pressure during verapamil infusion with a gradual recovery upon cessation of infusion. A decrease in arterial blood pressure was also noted in these animals.[2] In this study, verapamil was also shown to cause a significant decrease in the amplitude of esophageal contractions produced by direct vagal stimulation. It should be noted that the infusion dose used in this study (64 μg/kg/min) is considerably larger than maximal doses of this drug reported in human studies (21 μg/kg/min) and produced significant decreases in arterial blood pressure.

A subsequent study with verapamil was performed using intravenous infusions in chair-restrained, awake baboons.[3] Using dose-response studies, a dose of 80 μg/kg/min was shown to decrease LES pressures by 74%. In addition, both the amplitude and duration of the peristaltic contractions in the smooth muscle portion of the distal esophagus were significantly decreased (about 50%) during infusion. No effect was noted on the contraction patterns in the upper esophagus (striated muscle). Peristalsis was initiated by a small bolus of water placed in the posterior pharynx, thus more closely simulating a primary peristaltic response. As in the opossum studies, a significant decrease in arterial blood pressure was noted during the infusions. The maximum decrease in mean arterial pressure was approximately

From the Department of Medicine and Gastroenterology Section, Bowman Gray School of Medicine, Winston-Salem, North Carolina.

Address for reprints: Donald O. Castell, MD, Department of Medicine, Gastroenterology Section, Bowman Gray School of Medicine, Winston Salem, North Carolina 27103.

TABLE I Summary of Published Reports of Effect of Calcium-Channel Blocking Agents on Esophageal Contractions

	Drug	LES Effect	Amplitude Effect
Pharrmacologic Studies in Animals			
Animal			
Opossum[2]	Verapamil	↓	↓
Baboon[3]	Verapamil	↓	↓
Baboon[4]	Diltiazem	↓	↓
Pharmacologic Studies in Humans			
Type Patient			
Normal[9]	Nifedipine	↓	↓
Diffuse Spasm[9]	Nifedipine	↓	↓
Normal[10]	Diltiazem	None	None
"Nutcracker esophagus"[10]	Diltiazem	None	↓
Normal[11]	Nifedipine	↓	↓
Clinical Trials			
Type Patient (n)			Symptom Response
Achalasia (20)[13]	Nifedipine		++
Achalasia (15)[14]	Nifedipine		±
"Nutcracker esophagus" (9)[10]	Diltiazem		++ (no placebo)

LES = lower esophageal sphincter.

40%. In an attempt to establish that the esophageal contraction pressure changes were not secondary to the hypotension, a similar degree of hypotension was produced by serial bleeding of these animals. With up to 40% decrease in arterial pressure, no significant changes in esophageal pressures were produced. It was concluded that verapamil produced a significant action independently at both the esophageal smooth muscle and the vascular smooth muscle sites. In a subsequent report, the investigators also reported similar effects on esophageal contraction pressures in the baboon with intravenous infusions of diltiazem.[4]

These initial animal studies indicated that calcium blockers would decrease esophageal contraction pressures if given in sufficient amounts. The associated decreases in arterial blood pressure raised questions concerning the true potential for their clinical use and indicated the need for further studies with tolerable doses in man.

There are no reports at present on the effects of any of the calcium-entry blocking agents on contraction pressures in the remainder of the gastrointestinal tract or on secretory effects in animals.

The suggestion that agents that block calcium-entry into muscle cells might inhibit contractions of esophageal body musculature and LES is not unprecedented. Previous in vitro studies have identified an important role for intracellular calcium in esophageal smooth muscle contractions. Cohen and Green[5] have shown that muscle strips from the region of the LES in the opossum demonstrate a decrease in both peak force of contraction and maximum velocity of shortening in response to decrease in calcium concentration in the perfusing medium.[5] Similar in vitro studies by Fox and Daniel[6] demonstrated both decreased tone and diminished "off" contractions in muscle strips from the sphincteric region of the opossum esophagus when exposed to calcium-free solution. Other in vitro studies by deCarle et al[7] showed that decrease in calcium content produced a decrease in LES muscle tone and also abolished contraction of longitudinal muscle and "off" response contractions of circular muscle from the esophageal body. These in vitro observations support the in vivo responses found in more recent studies of calcium-entry blockade by verapamil and diltiazem.

Pharmacologic Studies in Humans

Calcium dependence of the contraction of human esophageal peristalsis in vivo has been previously demonstrated in normal volunteers by Danielides and Mellow.[8] In this study, calcium infusions producing significant increases in serum calcium concentrations resulted in a significant increase in the amplitude and the change in pressure with time (dP/dt) of esophageal peristaltic contractions in the smooth muscle esophagus. No effect was noted on the duration or velocity of peristaltic waves.

The first pharmacologic testing of a calcium-entry blocking agent in man was reported in 1981. In studies with nifedipine involving normal volunteers and patients with esophageal motility disorders, significant effects were observed on esophageal contractions. After an oral dose of nifedipine, 20 mg, significant decreases in resting LES pressure and in amplitude of peristaltic contractions were noted in normal subjects.[9] In addition, patients with diffuse esophageal spasm had significant decreases in LES pressure and peristaltic contraction amplitudes. These patients were also shown to have significant decreases in the amplitudes of their nonperistaltic "spastic" contractions and a decreased frequency of spontaneous "spastic" contractions. Although slight decreases in mean arterial blood pressure were noted, the patients did not have symptoms of hypotension.

In this same report, the investigators described their studies of the possible effect of nifedipine, 20 mg orally,

on gastric emptying. Dual-isotope labeling of both solid and liquid components of a meal was performed in normal subjects and patients who had prior gastric surgery. No effect of nifedipine on gastric emptying could be demonstrated.

In a recent study in our laboratory, we have measured the effect of diltiazem in a group of patients with recurring chest pain and high amplitude peristaltic contractions (the "nutcracker esophagus").[10] Significant decreases ($p < 0.05$) in both amplitude and duration of esophageal peristaltic contractions were found with single doses of 90 and 150 mg orally. These effects are illustrated in Figure 1. No significant decrease in systemic blood pressure was noted at these dose levels.

More recently, Hongo et al[11] have reported studies on the effects of nifedipine on esophageal contractions in normal subjects. Decreases in amplitude of esophageal peristalsis were reported with doses of 30 and 40 mg. No significant decrease in blood pressure was reported. These studies are summarized in Table I.

Recent preliminary studies in 10 patients with irritable bowel syndrome have shown that oral nifedipine, 20 or 40 mg, decreased colon motility.[12] Intraluminal rectosigmoid pressures measured during graded balloon distention were significantly decreased. Further studies were suggested to evaluate the therapeutic role of nifedipine in patients with irritable bowel.

To date there have been no reported studies on the effects of verapamil on gastrointestinal smooth muscle in man. Except for the aforementioned studies, there have been no reported human pharmacologic studies on the effects of these drugs either on contraction pressures in other areas of the gastrointestinal tract or on secretory functions.

The pharmacologic studies in animals and humans provide evidence that calcium-entry blocking drugs offer potential as therapeutic agents in conditions associated with excessive contractions of gastrointestinal smooth muscle, particularly in the esophagus.

Clinical Trials

Brief clinical trials of patients with esophageal motility disorders have been performed with calcium-blocking agents (Table I). To date, most of these trials involved nifedipine, although some data are available with diltiazem. Because of its characteristic pathophysiologic defect of very high LES pressure and incomplete relaxation during swallowing, achalasia is an entity in which these drugs have potential therapeutic value. In 1 placebo-controlled trial, the effect of nifedipine (10 to 20 mg sublingually 30 minutes before meals) was evaluated in 20 patients with achalasia. When studied for a period of up to 18 months, "excellent or good results" were noted in most patients evaluated by clinical grading of symptoms including dysphagia, chest pain and weight loss. The clinical improvement with nifedipine was significantly greater than that noted with placebo. This study suggested that nifedipine might be used in the medical treatment of patients with mild-to-moderate achalasia.[13]

A subsequent study compared the effect of nifedipine with isosorbide dinitrate in the treatment of achalasia.[14] In a crossover study design, 15 patients were treated with both nifedipine (10 mg orally 30 minutes before meals) or isosorbide dinitrate (5 mg sublingually 10 minutes before meals). Subjective improvement in dysphagia was reported in 13 patients receiving nitrate and only 8 receiving nifedipine. Headache and other adverse effects were more prominent during nitrate therapy. This study was only mildly enthusiastic about the potential effectiveness of nifedipine in the treatment of achalasia, reporting a better effect with nitrate therapy. It is quite difficult to draw any major conclusion concerning medical therapy of achalasia from this study.

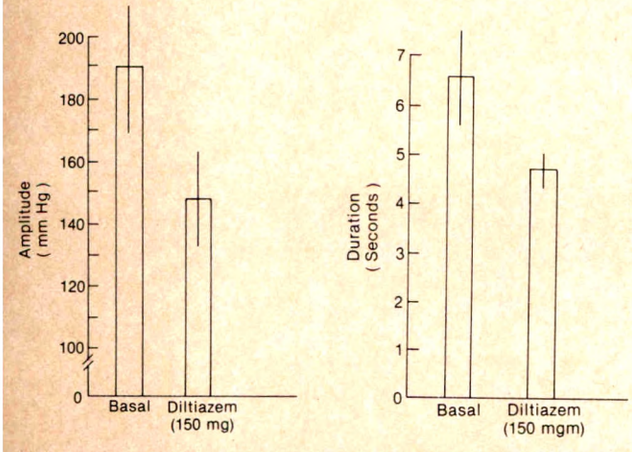

FIGURE 1. Left, mean amplitude of esophageal peristaltic contractions in 10 patients with high amplitude peristalsis ("nutcracker esophagus") before (Basal) and 120 minutes after a single oral dose of diltiazem (150 mg). Vertical lines indicate ± standard error of the mean. A significant decrease ($p < 0.05$) in mean amplitude occurred. **Right,** mean duration of esophageal peristaltic contractions in 10 patients with nutcracker esophagus both before (Basal) and 2 hours after an oral dose of diltiazem (150 mg). Vertical lines indicate ± standard error of the mean. A significant decrease ($p < 0.05$) in mean wave duration occurred.

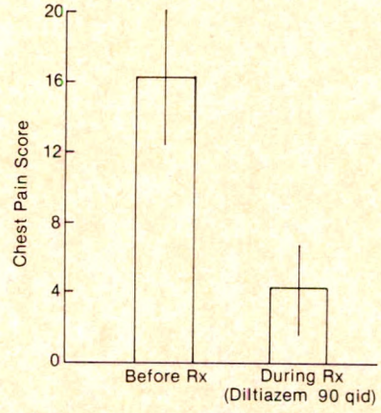

FIGURE 2. Mean chest pain score in 9 patients with nutcracker esophagus obtained before therapy and during an 8-week trial of diltiazem (90 mg 4 times daily). Score was obtained from the product of intensity and frequency of chest pain during each week of therapy. From a maximum potential value of 6 for each factor, a maximum potential score of 36 was possible. Mean values are shown from the group during week before therapy and during eighth week of treatment. The vertical lines indicate ± 1 standard error of the mean. A significant decrease ($p < 0.05$) in mean pain score occurred.

We have obtained preliminary observations on the use of diltiazem in the treatment of patients with the nutcracker esophagus.[10] Over an 8-week study period, significant improvement in incidence and severity of recurring chest pain was noted in 9 patients treated with diltiazem, 90 mg 4 times daily (Fig. 2). The results of this uncontrolled study were quite encouraging and a placebo-controlled trial is currently underway.

There is minimal information available in the potential therapeutic effects of calcium-channel blocking agents in other gastrointestinal disorders. Because of the profound effect of these agents on esophageal smooth muscle, it is reasonable to speculate that similar actions would occur in smooth muscle in other areas of the gastrointestinal tract, particularly in the colon. Likewise, because of the dependence of many secretory processes on intracellular calcium, one might readily propose that excessive secretory conditions might respond to drugs of this kind. These observations have led to speculations, and some empirical trials, of the efficacy of calcium-channel blocking agents in the therapy of a number of other gastrointestinal conditions, including irritable bowel syndrome, gastric hypersecretory states, acute pancreatitis and various diarrheal states. The role of calcium-blocking agents in the treatment of gastrointestinal disorders involving abnormal contraction patterns or abnormal secretion has received limited study at present. There are exciting potential uses for these drugs in a number of gastrointestinal disorders that remain to be explored.

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Second-Generation Calcium Antagonists: Search for Greater Selectivity and Versatility

BRAMAH N. SINGH, MD, DPhil, SHERRIN BAKY, MS,
and KOONLAWEE NADEMANEE, MD

Calcium antagonists have a variable specificity for cardiac and peripheral activity. Based on such activity, these compounds, new and old, can be classified into 4 categories. Type 1 agents, typified by verapamil, its congeners (tiapamil and gallopamil) and diltiazem, prolong atrioventricular nodal conduction and refractoriness with little effect on ventricular or atrial refractoriness. These actions, to a large extent, account for the antiarrhythmic properties of this type of calcium antagonists. Type 2 agents include nifedipine and other dihydropyridines. In vivo, these agents are devoid of electrophysiologic effects in usual doses and concentrations. They are potent peripheral vasodilators with some selectivity of action for different vascular beds; their overall hemodynamic effects are dominated by this peripheral vasodilatation and reflex augmentation of sympathetic reflexes. Type 3 agents are flunarizine and cinnarizine (piperazine derivatives); in vitro and vivo, they are potent dilators of peripheral vessels, with no corresponding calcium-blocking actions in the heart. Type 4 agents (perhexiline, lidoflazine and bepridil) have a broader pharmacologic profile; they block calcium fluxes in the heart, in the peripheral vessels or in both. They may inhibit the fast channel in the heart and have other electrophysiologic actions. A clear understanding of the varied pharmacologic properties of the different classes of calcium antagonists is likely to provide a rational basis for the use of the newer agents in clinical therapeutics. Future development may produce agents with a greater tissue selectivity on the one hand and a broader pharmacologic profile and therapeutic spectrum of activity on the other.

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Although more than 20 years have passed since the prototype of calcium antagonists was introduced, rapid advances in our understanding of the pharmacodynamic effects of these agents and their clinical applications followed only after Fleckenstein[1,2] provided important conceptual framework in the early 1970s. The pioneering work focused attention on the selectivity of effects of calcium antagonists on the myocardial slow channel, most readily demonstrable in isolated preparations using the voltage clamp technique.[3] The electrophysiologic effects of such agents as verapamil and prenylamine[2] in cardiac muscle were found to be similar to those produced by calcium-free media. The slow channel could be blocked to a substantial degree with concentrations of the drugs that had little or no effect on the fast sodium channel. Agents with this selectivity of myocardial action also had the propensity to block calcium fluxes in vascular smooth muscle; thus, they were all peripheral and coronary vasodilators. It soon became clear, however, that the so-called calcium-antagonist compounds (defined primarily as those agents that produced excitation-contraction uncoupling in cardiac muscle by blocking the slow channel) manifested a bewildering heterogeneity in chemical structure and were not completely selective for the myocardial slow channel. Some agents were truly selective for the slow channel in extremely low concentrations (for example, the dihydropyridines), and others blocked the slow as well as the fast channel in approximately the same drug concentrations (such as perhexiline). An appreciation of these differences led Fleckenstein[2,4] to divide calcium antagonists into 2 categories, but these may no longer be adequate to account for the diversity of effects of all calcium antagonists, new and old. For example, there appear to be differences in the potencies

From the Department of Cardiology, Wadsworth Veterans Administration Hospital, and the Department of Medicine, UCLA School of Medicine, Los Angeles, California. This study was supported in part by grants from the Medical Research Service of the Veterans Administration and from the American Heart Association, the Greater Los Angeles Affiliate.

Address for reprints: Bramah N. Singh, MD, PhD, FRCP, Section of Cardiology 691/111E, Wadsworth Veterans Administration Hospital, Wilshire and Sawtelle Boulevard, Los Angeles, California 90073.

of individual calcium antagonists with respect to their ability to block the slow channels in both cardiac and smooth muscle. Whereas a truly cardioselective agent (that is, one that blocks the slow channel in the heart and has no effect on vascular smooth muscle) has not been reported, the converse has been. For example, cinnarizine and flunarizine in vivo appear to competitively antagonize calcium fluxes in vascular smooth muscle; yet they have no effect on cardiac muscle in the same concentrations.[5] In addition, whereas lidoflazine also selectively inhibits the slow channel in vascular smooth muscle as opposed to the myocardial slow channel, it has the added propensity of blocking the fast channel in the heart.[6] Another dimension of complexity has been identified by radioligand binding studies,[7] which have demonstrated that different calcium antagonists display a diverse spectrum of antagonism toward selective tissues, a phenomenon that may have far-reaching therapeutic possibilities.

This report provides an expanded and clinically relevant classification of calcium antagonists as a framework for the discussion of the properties of some of the newer therapeutic agents that are promising and are likely to be introduced in the United States in the near future.

Classification of Calcium Antagonists

In 1977, Fleckenstein[4] suggested that calcium antagonists could be classified into 2 categories. He placed such agents as verapamil, diltiazem and nifedipine and its derivatives, which have a marked selectivity for inhibiting the slow channel versus the fast sodium channel in the heart, into 1 group. He placed such agents as prenylamine, terodiline, fendiline and perhexiline, which also inhibit the slow channel but have a broad array of other electrophysiologic actions, into another group. However, the expanding knowledge of the electropharmacologic features of these and newer agents suggests a need for an alternative classification. The one proposed in Table I was developed along clinical lines. It, too, may eventually need modification because the clinical and experimental data relating to calcium antagonists continue to increase rapidly.

As outlined in Table I, it appears useful to create 1 category for those calcium antagonists that impede conduction across the atrioventricular (AV) node and prolong its refractoriness in vivo. Such compounds include verapamil and its congeners (gallopamil and tiapamil) as well as diltiazem (Fig. 1). Electrophysiologically, these agents have qualitatively (but not necessarily quantitatively) similar effects and are thus likely to have a similar spectrum of antiarrhythmic properties. They are of particular value in the treatment of certain supraventricular tachyarrhythmias. These drugs also have the capacity to depress myocardial contractile function in vivo.

The second proposed class of calcium antagonists (Fig. 2) is represented by the numerous dihydropyridine derivatives (nifedipine, nitrendipine, nisoldipine, nimodipine, niludipine and nicardipine). These agents exert a depressant effect on sinus nodal frequency and inhibit AV conduction in vitro but not in vivo. Because all are potent peripheral vasodilators, the unopposed reflex increases in heart rate, AV conduction and contractility that they produce have a significant effect on the overall hemodynamic and electrophysiologic properties of these compounds. The dihydropyridine derivatives may be extremely effective as afterload-reducing agents in the control of certain hypertensive

TABLE I Clinical Classification of Calcium Antagonists

Type 1: Calcium antagonists with in vivo myocardial, electrophysiologic and vascular effects
Verapamil
Gallopamil (D-600)
Diltiazem
Tiapamil
Type 2: Calcium antagonists with predominant vascular effects in vivo
Nifedipine
Nitrendipine
Nisoldipine
Nimodipine
Nicardipine
Niludipine
Felodipine
Type 3: Calcium antagonists with selective vascular effects
Cinnarizine
Flunarizine
Type 4: Calcium antagonists with complex pharmacologic profile
Bepridil
Lidoflazine
Perhexilene

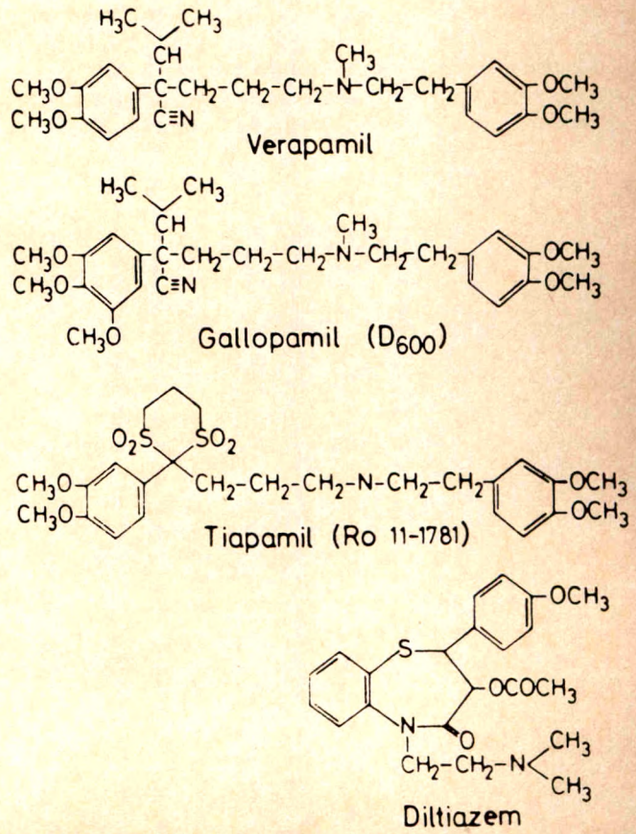


FIGURE 1. Chemical structure of type 1 of calcium antagonists, which exert effects on atrioventricular conduction and refractoriness in vivo without significant effect on ventricular refractoriness. Note that verapamil and its congeners (tiapamil, gallopamil) differ in structure.

emergencies.[8] Conversely, because of the unopposed reflex effects, especially tachycardia and augmented contractility, they may aggravate myocardial ischemia in patients with fixed coronary lesions. These drugs also have the potential to depress myocardial contractile function in vivo but they are much less potent in this regard than the type 1 agents.

The third type of calcium antagonists (Fig. 3), characterized by the piperazine derivatives cinnarizine and flunarizine, may be regarded as having "reversed" specificity insofar as they appear to have few or no direct myocardial effects while having the propensity to block calcium movements in the peripheral vascular smooth muscle cells. It may even be argued whether these agents are calcium antagonists in the sense first conceived by Fleckenstein,[1] but pharmacologically it appears acceptable to view these compounds as having unique selectivity for vascular tissues.

Finally, there is a heterogeneous group of compounds (Fig. 4) that in certain concentrations block the myocardial slow channel and dilate the peripheral and coronary vessels, but also have other complex electrophysiologic actions. For example, perhexiline blocks both the fast and the slow channels in the heart at approximately the same concentrations. It uses one mechanism to increase the effective refractory period of tissue dependent on the slow channel for depolarization and another for tissue dependent on the fast channel. This agent is thus likely to have a wider spectrum of antiarrhythmic activity than those drugs that act solely from effects on the slow channel. In contrast, lidoflazine has no significant effect on the slow channel in the heart while it does have such an effect in vascular smooth muscle; it inhibits the fast channel and, like quinidine, has a modest effect in lengthening the action potential duration in ventricular muscle and Purkinje fibers. Perhaps the most complex pharmacologic actions are exerted by the drug bepridil. Bepridil appears to have the myocardial and peripheral effects of such type 1 compounds as verapamil. Yet it also inhibits the fast sodium channel while lengthening the action potential duration in most cardiac tissues. Thus, bepridil has the propensity to increase the voltage as well as the time-dependent refractoriness in the conducting and working fibers of the heart, while its effect on the slow channel in the slow-channel dependent tissues is similar to the electrophysiologic properties of verapamil. Calcium antagonism is therefore only one feature, albeit an important one, in the pharmacologic properties of this type of calcium antagonists.

A detailed appreciation of the net pharmacologic effects of these varied compounds will permit the rational basis for their clinical utility to be established. What follows is a discussion of the properties of some of the newer compounds, with the emphasis on recent developments particularly relevant to the expanding therapeutic roles of calcium antagonists in cardiovascular disease.

Type 1: Calcium Antagonists with In Vivo Myocardial Effects

The chemical structures of diltiazem, tiapamil and gallopamil (D-600) are shown in Figure 1 relative to that of the reference calcium antagonist, verapamil. Except for diltiazem, there are structural similarities among the other 3 compounds. All 4 are moderately potent peripheral vasodilators and are likely to have significant clinical utility in the control of mild-to-moderate essential hypertension. Their predominant electrophysiologic actions are lengthening conduction time and prolonging refractoriness in the AV node, properties that account for their known antiarrhythmic effects. The hemodynamic effects of verapamil in experimental

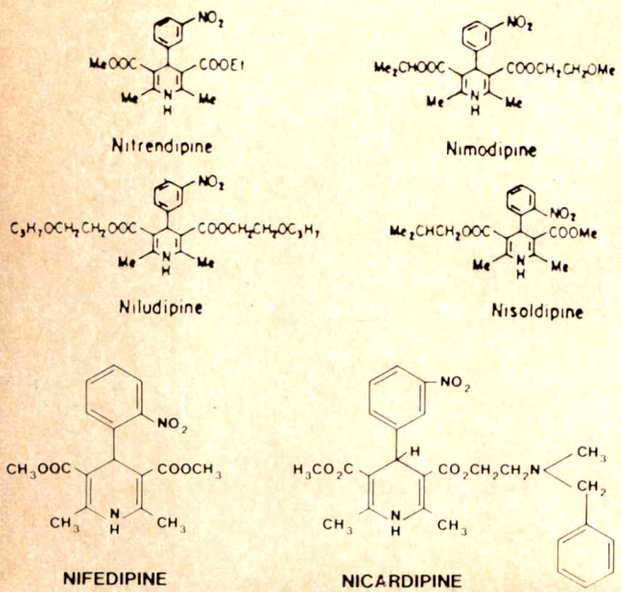


FIGURE 2. Chemical structure of some of the dihydrophridines, type 2 of calcium antagonists. Note that a minor difference in the structure may lead to variations in pharmacologic properties (see text). This category of calcium antagonist offers the greatest scope for studying structure-activity relations.

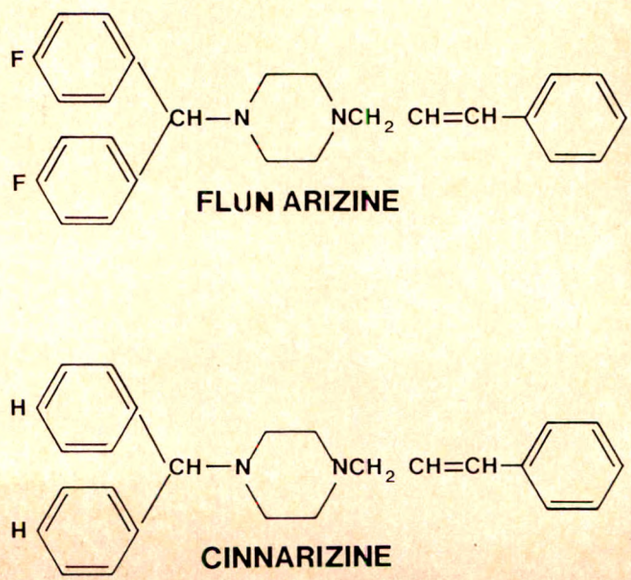


FIGURE 3. Structure of flunarizine and cinnarizine, type 3 of calcium antagonists. These agents have a specificity for vascular tissues.

animals and in patients with varying levels of ventricular function are reasonably well defined; there are modest data for diltiazem and very little for either tiapamil or gallopamil. Although unpublished data have suggested that gallopamil might be extremely effective in terminating supraventricular tachycardias and in controlling chronic stable angina, further data are needed to determine the comparative efficacy of tiapamil and gallopamil on the one hand and verapamil and diltiazem on the other. Neither tiapamil nor gallopamil is currently under investigational evaluation in the United States.

Type 2: The Dihydropyridine Subgroup of Calcium Antagonists

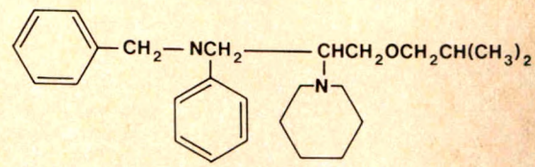
Numerous dihydropyridine derivatives are currently under investigation for the control of a variety of cardiocirculatory disorders, depending upon each drug's presumed specific pharmacologic properties. Of the newer compounds, dihydropyridine derivatives are the most closely related structurally. As a group, the potency of the dihydropyridines is much greater in relation to smooth muscle compared with cardiac muscle. These agents, in vivo, are nearly or completely devoid of clinically significant electrophysiologic properties; their overall hemodynamic effect is dominated by striking peripheral vasodilatation. From the therapeutic standpoint, this may prove of particular value in the control of hypertensive emergencies as well as in the long-term management of essential hypertension, either as single agents or in combination with diuretics, β-adrenergic blocking drugs or other hypotensive agents. It is emphasized that because all of these agents produce marked reflex increases in heart rate and contractility, angina may be aggravated in some patients with coronary artery disease if concomitant sympatholytic agents are not used.

The dihydropyridines may exert tissue selectivity but little data on structure-activity relation are available to document such a predilection.[9] However, it appears that the ester-substituted analogues of nifedipine exhibit a greatly enhanced smooth muscle selectivity relative to nifedipine.[9,10] For example, both niludipine and nisoldipine are more potent than nifedipine as vasodilators, but in vitro all have the same cardiac activity.[9] Substitution at the ester position of the 1,4-dihydropyridine series may be a significant probe for differences in binding site organization or channel function in cardiac and smooth muscle.[11] Whether it might be possible to demonstrate such differences among the smooth muscles of regional vascular beds is at present uncertain, although preliminary data suggest that nimodipine might have selectivity of action in the cerebral vasculature.[10]

Nimodipine: Nimodipine increases cerebral blood flow[10] with salutary effects in experimental models of subarachnoid hemorrhage, cerebral ischemia and stroke.[11–16] In a double-blind study when the drug was infused intravenously during external carotid to internal carotid bypass surgery in 16 patients,[17] it produced a significant dilatation of pial arteries with resting diameters from 25 to 70 μm. Nimodipine was also found effective in preventing neurologic complications after ruptured cerebral aneurysm.[18] Furthermore, in a prospective, double-blind, randomized, placebo-controlled trial performed in the United States, nimodipine significantly decreased the occurrence of severe neurologic deficits from arterial spasm after subarachnoid hemorrhage. It is also noteworthy that nimodipine (40 mg 3 times a day) had significant beneficial effects on the frequency of migraine attacks and their duration during a 2-month, double-blind, placebo-controlled parallel study in 60 patients;[20] negligible adverse effects were attributable to the drug.

Nitrendipine: Animal studies have documented a pronounced antihypertensive activity for nitrendipine.[21] A single-dose (20 mg orally) study in patients with mild essential hypertension[22,23] showed that the immediate antihypertensive effect was associated with a significant decrease in total peripheral vascular resistance and an increase in heart rate, cardiac output and left ventricular ejection rate in 7 of the 12 study patients who responded to the drug. No postural hypotension developed. In another hemodynamic study,[24] 20 mg orally of nitrendipine, decreased arterial pressure from 225/105 to 177/81 mm Hg within 3 hours as a result of a significant decrease in total peripheral resistance. Clinical trials have suggested that nitrendipine is an effective antihypertensive agent at dosages ranging from 20 to 40 mm/day.[25,26] At the higher dose, there were reports of headache, flushing, tachycardia and palpitations; these effects are consistent with the drug's peripheral vasodilator actions being more marked as the dose is increased.

Nisoldipine: Nisoldipine has a preferential action



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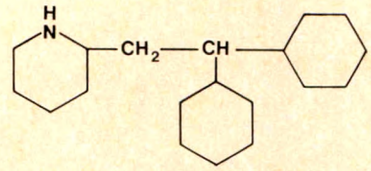

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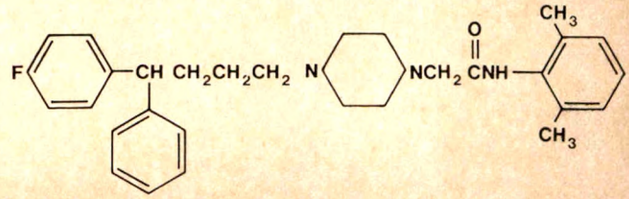

LIDOFLAZINE

FIGURE 4. Chemical structure of 3 calcium antagonists with a broad pharmacologic profile, type 4 of calcium antagonists. Note striking differences in their structure.

on vascular smooth muscle,[27] but a complete profile of its pharmacodynamic activity has not been delineated. Hemodynamic studies in man after the administration of intravenous nisoldipine have shown a decrease in arterial pressure, total peripheral resistance accompanied by an increase in cardiac output and heart rate and no significant change in the maximum first derivative of left ventricular pressure (dP/dt_{max}).[28]

In hypertensive patients given 5, 10 and 20 mg oral doses, arterial pressure decreased in a dose-dependent manner;[27] this effect was accompanied by an increase in heart rate. The hypotensive effect lasted for 10 hours, indicating a relatively long elimination half-life of the drug. Nisoldipine has no significant electrophysiologic effects in man.[29] In patients with congestive heart failure (New York Heart Association class III), 20 mg of the oral drug improved the hemodynamic status by simultaneously reducing the preload and afterload[30] induced by peripheral vasodilatation with diminished peripheral vascular resistance. Further clinical evaluation of nisoldipine is thus indicated.

Nicardipine: This compound is currently undergoing extensive evaluation in patients with angina pectoris and hypertension in the United States and Europe. In several double-blind, placebo-controlled studies, each using the same protocol design[31] the effects of nicardipine (40 mg) were compared with those of diltiazem (120 mg), nifedipine (20 mg), verapamil (120 mg) and propranolol (80 mg), all administered 3 times a day for 4 weeks. All the drugs increased the duration of treadmill exercise and time to 1 mm ST-segment depression; in the doses used, nicardipine and nifedipine were similar to propranolol, whereas diltiazem and verapamil appeared to be superior. Gheorgiade et al[32] recently provided data clearly documenting the superiority of nicardipine over placebo.

In the first double-blind, placebo-controlled study of nicardipine in patients with angina at rest and coronary spasm, Gelman et al[33] found the drug effective and well-tolerated. The average weekly frequency of anginal attacks and nitroglycerin consumption was decreased in these patients, who had previously been refractory to other calcium blockers.

Several double-blind, parallel, placebo-controlled studies[31,34] have shown that nicardipine significantly decreases blood pressure in hypertensive patients. The hypotensive effects of the drug have been further studied in 18 patients undergoing intraarterial 24-hour ambulatory blood pressure monitoring[35] before and after at least 6 weeks of drug therapy (40 mg twice a day). Patients had moderate-to-severe hypertension (direct blood pressure recording of 160/100 mm Hg for 6 hours on a 24-hour recording) at baseline. Blood pressure was controlled by nicardipine throughout the day, including during exercise and cold challenge. The mean daytime intraarterial blood pressure was significantly decreased by 17/8 mm Hg. However, 4 patients had to be withdrawn from the study because of adverse effects.

Because it appeared to be a potent and long-lasting dilator of cerebral vasculature in animals,[36] the safety and efficacy of nicardipine in the treatment of patients with various cerebral vasculature disorders, especially the sequelae of cerebral hemorrhage and stroke have been investigated in Japan in double-blind clinical trials.[32] It is believed that the drug is effective, but further clinical trials are necessary for confirmation and to determine the relative effectiveness of various calcium antagonists in this setting.

Type 3: The Piperazine Derivatives Flunarizine and Cinnarizine

The properties of the compounds in this type of calcium antagonist, namely cinnarizine and its difluro derivative flunarizine, are highly selective for calcium channels in vascular smooth muscle relative to cardiac muscle.[37] For example, Nakayama and Kasuya[38] showed that the relaxation of potassium-induced contracture of the rabbit basilar artery (ED_{50} 0.12 μmol/liter; relative potency 1) induced by flunarizine was much more than its inhibition of isometric tension of the rabbit papillary muscle (ED_{50} 75 μmol/liter; relative potency 625).

The properties and therapeutic uses of flunarizine were recently reviewed by Holmes et al.[39] Flunarizine has a much longer plasma elimination half-life than does cinnarizine. Most of the therapeutic trials with flunarizine involved the prophylaxis of migraine, occlusive peripheral vascular disease and vertigo of central and peripheral origin. The data from placebo-controlled studies indicate that flunarizine is more effective than placebo in these conditions when evaluated by subjective and objective criteria.[40–50] Prophylactic protection of flunarizine has been reported in patients with migraine;[43–45] 1 double-blind study[46] has indicated that flunarizine suppressed the severity of migraine attacks and significantly reduced the number of episodes. Symptoms of vertebrobasilar insufficiency were found improved in 20 patients given flunarizine, 20 mg/day for 8 weeks, in another study.[47] Objective parameters were measured using electroencephalography, electronystagmography and Doppler sonography; results correlated well with symptomatic improvement. There was a subsequent double-blind, placebo-controlled, crossover trial using 10 mg/day of flunarizine in 41 patients with vertigo.[48] After a 4-week run-in period, 40 responders were randomized to either continued treatment or placebo. After 6 weeks, the patients were crossed-over to the alternative therapy. The administration of placebo significantly worsened the patients' condition. Flunarizine did not significantly decrease tinnitus.

Another study showed that flunarizine (10 to 20 mg/day for 6 months) improved Doppler flowmeter readings and increased independent mobility in patients with arteriopathies of the lower extremities. In 4 double-blind, placebo-controlled studies in patients with venous insufficiency (varicose veins and venous ulcers), flunarizine, 10 mg/day, significantly improved symptoms, reduced the circumference of swollen legs and ankles and increased the speed of healing of venous ulcers in the legs.[50]

These preliminary data with the piperazine derivatives suggest new and useful pharmacologic approaches to the control of several circulatory disorders, but the precise role of these compounds in therapy must await results of further stringently controlled comparative studies.

Type 4: Calcium Antagonists with Complex Pharmacologic Profiles

The fourth group of pharmacologic agents may be categorized as calcium antagonists that have a selectivity of action either for vascular tissues (for example, lidoflazine) or (in the case of perhexiline[51–53] and bepridil[54]) for both cardiac and smooth muscle, while they also have the propensity to block the fast sodium channel in the heart to a variable degree. Some of these agents have still other electrophysiologic properties. These agents are not only heterogeneous chemically but, by virtue of their overall complex pharmacologic properties, they may exert a somewhat different spectrum of therapeutic effects. This pertains particularly to their cardiac electrophysiologic actions and to the control of cardiac arrhythmias.

Lidoflazine: Like flunarizine and cinnarizine, lidoflazine is a piperazine derivative. With them, it shares the property of relaxing vascular smooth muscle in the coronary arteries and peripheral vessels by competitively blocking calcium transport. Thus, it can be regarded as a calcium antagonist even though it does not inhibit the slow channel in cardiac tissues. However, unlike flunarizine and cinnarizine, lidoflazine blocks the fast sodium channel in cardiac muscle and lengthens repolarization. In vitro data indicate that, in relatively small concentrations under voltage clamp conditions, the drug does not block the myocardial slow channel.[54] Thus, even in high doses lidoflazine has no significant negative inotropic effect in patients with angina pectoris.[55,56] Lidoflazine does not alter heart rate at rest, but it does increase the duration of treadmill exercise in patients with angina pectoris while delaying the onset of ST-segment depression.[56] Lidoflazine is a potent coronary dilator[57] and has the propensity to ameliorate perfusion deficits induced by treadmill exercise in patients with coronary artery disease.[56] The available data suggest that the antianginal effects of the drug in various myocardial ischemic syndromes are likely to be similar to those of other calcium antagonists.

Scant information is available regarding the electrophysiologic effects of lidoflazine in man. However, it has been shown to prolong the QTc interval in the surface electrocardiogram in a clinical study.[58] The properties of the compound appear to be similar to quinidine and quinidine-like drugs with potential for antiarrhythmic as well as arrhythmogenic effects. Neither of these features has so far been studied in detail, although anecdotal cases of torsade de pointes accompanied by syncope have been described in association with the therapeutic use of lidoflazine.

Bepridil: This is perhaps the most promising of the type 4 agents. Unlike other calcium antagonists, bepridil has a long elimination half-life (almost 40 hours).

Electrophysiologically, bepridil is unusual: it blocks the slow calcium channel in the heart,[59] while it inhibits the fast channel and lengthens the repolarization phase of the cardiac action potential in all myocardial tissues with the possible exception of Purkinje fibers. These data are consistent with preliminary clinical observations;[60] intravenous bepridil prolonged the effective refractory period of atria, ventricles and AV node, while lengthening the Wenckebach cycle of the AV node during rapid atrial pacing. The spontaneous sinus cycle length was not significantly altered nor was the sinus nodal recovery time, although patients with sick sinus disease were not studied. The AH interval was prolonged with a trend toward an increase in the HV interval during electrophysiologic studies.

The available data suggest that unlike most other calcium antagonists, bepridil is likely to be effective in ventricular and supraventricular tachyarrhyhthmias, although the relative potencies of the compound in these 2 groups of dysrhythmias remain to be determined. Preliminary data on the prevention of ventricular tachycardia induced by progammed electrical stimulation of the heart are conflicting;[61] data on the suppression of premature ventricular contraction also need further documentation. It should be emphasized that because the overall properties of bepridil in ventricular muscle resemble those of quinidine, the compound may produce torsade de pointes in toxic doses or when it is used in the setting of hypokalemia or hypomagnesemia.

When bepridil was given intravenously to dogs, coronary vascular resistance decreased and coronary blood flow increased.[62] In patients with chronic stable angina,[63] bepridil exerts significant antianginal efficacy with respect to reduction in nitroglycerin consumption and anginal frequency. Narahara et al,[64] in a single-blind, 20-patient, placebo-controlled study, (in 13 with resting and exercise radionuclide ventriculography) showed that bepridil (up to 300 mg/day orally), significantly decreased anginal frequency and increased total work performed on upright bicycle. The exercise duration increased from 5.3 to 6.6 minutes ($p < 0.005$) and the expected deterioration in left ventricular function induced by exercise was prevented. A recent multicenter study has further documented the antianginal efficacy of bepridil in chronic stable angina[65] and a smaller study[66] has shown that the drug has the capability to reduce the duration of painless as well as pain-related ischemia in patients with chronic stable angina studied by ambulatory Holter recordings analyzed by the compact analogue technique.[67]

At present, the comparative antianginal and antiischemic efficacy of bepridil and other calcium antagonists is not well defined, nor are the issues of the safety and efficacy of a bepridil–β-blocker combination resolved. However, the available data indicate that bepridil may develop into a calcium antagonist with a wide spectrum of use. Its pharmacologic properties and therapeutic potential compared with its adverse effect profile (that is, its arrhythmogenic propensity) should be further evaluated.

In summary, we have reviewed data on the newer calcium antagonists that hold promise in cardiovascular therapeutics and offer several conclusions. First, although the conceptual framework for characterizing calcium antagonists postulated by Fleckenstein provided an important impetus for the development of calcium antagonist therapy, refinements in his original concept are now needed to allow for a systematic understanding of the newer compounds. Second, classification of the available compounds based on an understanding of their specificity for cardiac and smooth muscle appears to have some clinical relevance. However, structure-activity relations within groups may reveal further differences that might be of therapeutic value. Third, the fact that there are marked structural differences among different calcium antagonists, old and new, means each agent needs to be studied experimentally and clinically to define its precise role in human therapeutics. Finally, based on the available information, it is reasonable to assume that further advances—in the development of both tissue-selective calcium-channel antagonists and calcium-channel antagonists with a broad pharmacologic profile and therapeutic spectrum of activity—are imminent.

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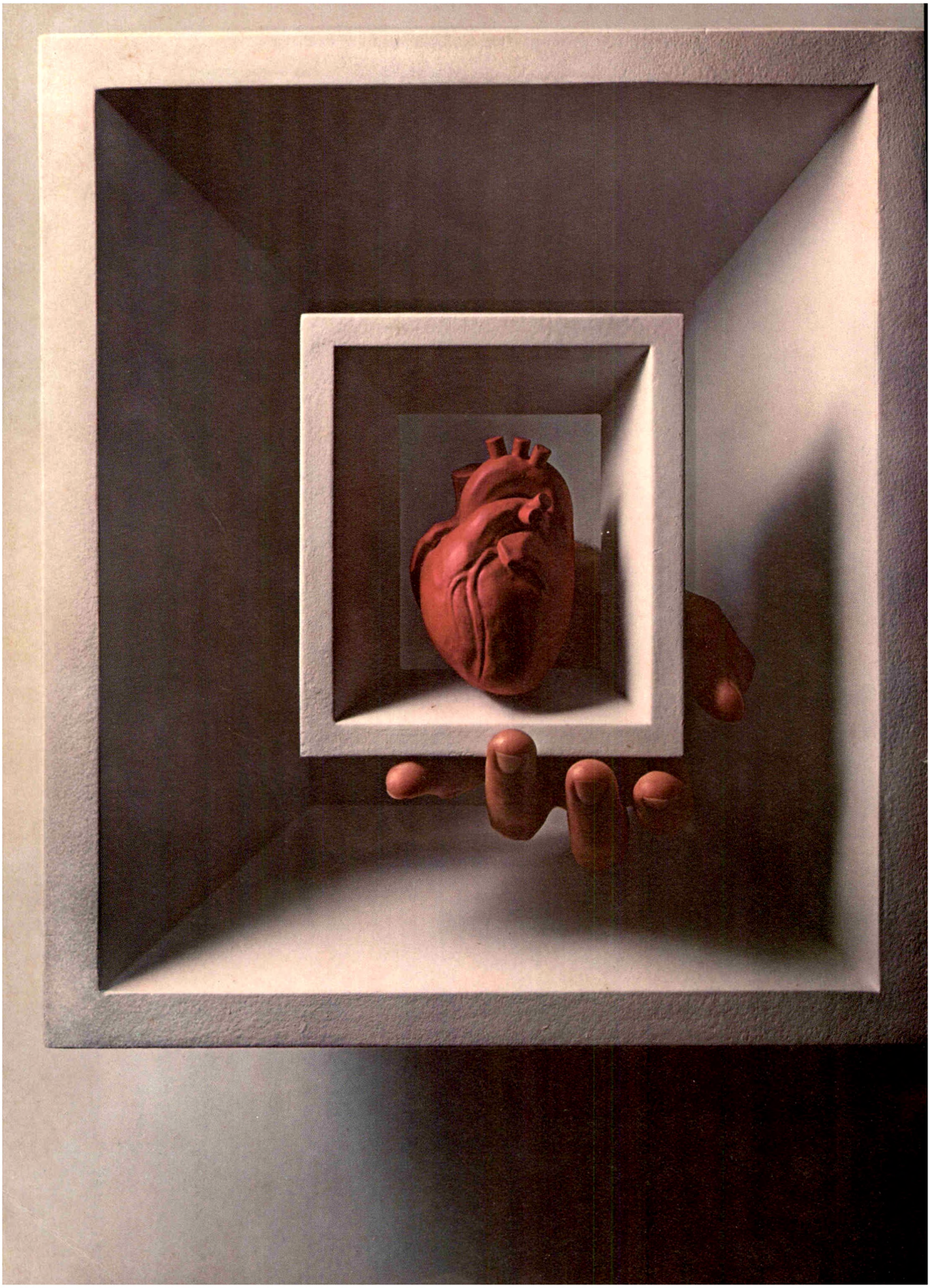

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Unlike calcium blockers, INDERAL LA—either alone or with a nitrate—is recommended for early treatment of angina in the majority of patients. Equally important, INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use.

START WITH 80 MG ONCE DAILY

Dosage may be increased to 160 mg once daily, as needed, to achieve optimal control. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY **INDERAL® LA**
(PROPRANOLOL HCl) *LONG ACTING CAPSULES*

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The appearance of INDERAL LA capsules is a registered trademark of

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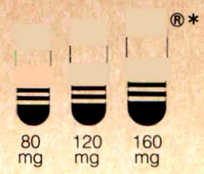
ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migrai..e: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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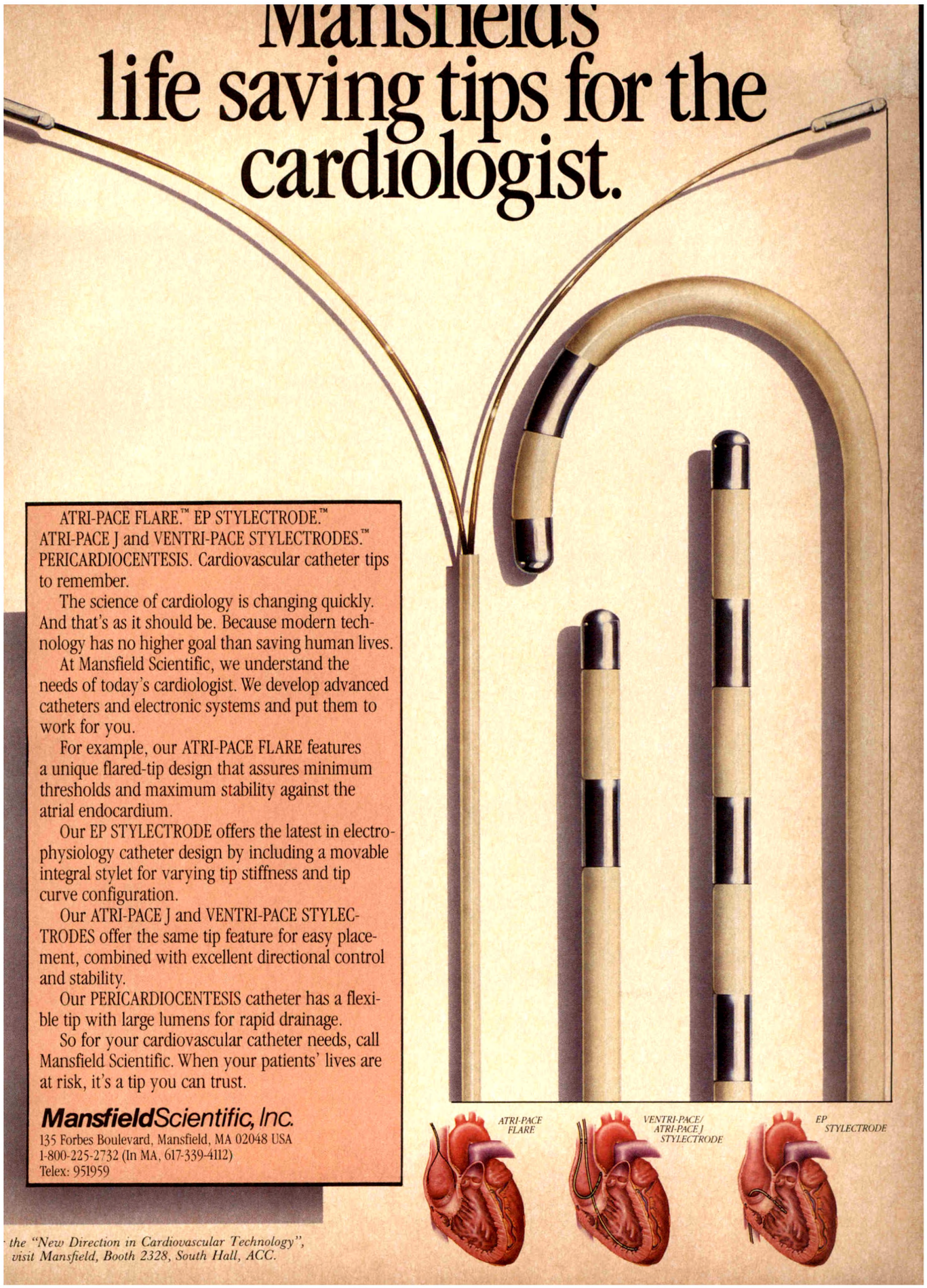

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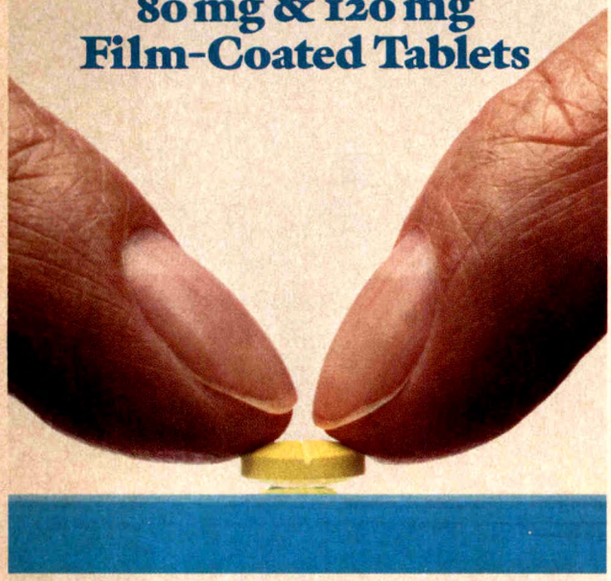

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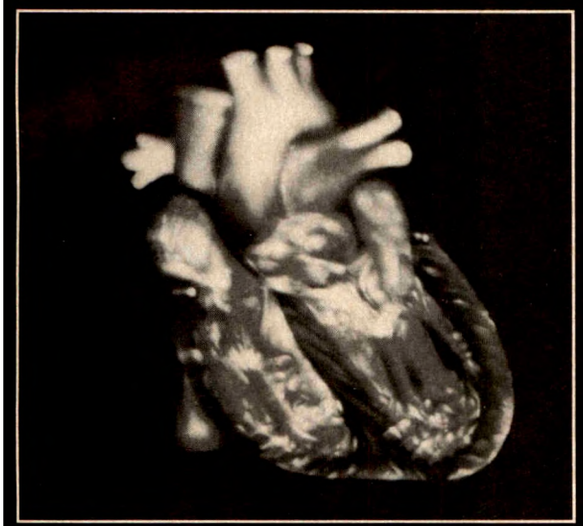

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dolol Tablets

SCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor cking agent.

)NTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first gree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

ARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component pporting circulatory function in congestive heart failure, and its inhibition by beta- ckade may precipitate more severe failure. Although beta-blockers should be avoided overt congestive heart failure, if necessary, they can be used with caution in patients h a history of failure who are well-compensated, usually with digitalis and diuretics. a-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart scle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of a-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or mptom of heart failure, digitalize and/or give diuretics, and closely observe response, discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — TIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE TA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation duced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to ex stimuli and may increase risks of general anesthesia and surgical procedures, ulting in protracted hypotension or low cardiac output, it has generally been suggested t such therapy should be withdrawn several days prior to surgery. Recognition of the reased sensitivity to catecholamines of patients recently withdrawn from beta-blocker rapy, however, has made this recommendation controversial. If possible, withdraw a-blockers well before surgery takes place. In emergency surgery, inform the esthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists h as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of dolol. Difficulty in restarting and maintaining the heart beat has also been reported h beta-adrenergic receptor blocking agents.

ance of premonitory signs and symptoms (e.g., tachycardia and bl of acute hypoglycemia. This is especially important with labile di also reduces release of insulin in response to hyperglycemia; necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certa tachycardia) of hyperthyroidism. To avoid abrupt withdraw blockade which might precipitate a thyroid storm, carefully manag developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Us in presence of either of these conditions (see DOSAGE AND ADM of package insert).

Information for Patients — Warn patients, especially th coronary artery insufficiency, against interruption or discontinuat physician's advice. Although cardiac failure rarely occurs in prop advise patients being treated with beta-adrenergic blocking agents first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., re additive effect when given with beta-blocking agents. When t nadolol plus a catecholamine-depleting agent, carefully observe tension and/or excessive bradycardia which may produce vertigo hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility - toxicologic studies in mice, rats, and dogs, nadolol did not pro effects. In 2-year oral carcinogenic studies in rats and mice, na neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evi fetotoxicity was found in rabbits (but not in rats or hamsters) at dose (on a mg/kg basis) than maximum indicated human dose; no tera seen in any of these species. There are no well-controlled studies therefore, use nadolol in pregnant women only if potential benefit to the fetus.

Nursing Mothers — It is not known whether this drug is exc Because many drugs are excreted in human milk, exercise cau administered to a nursing woman. Animal studies showed that n milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have no

ADVERSE REACTIONS: Most adverse effects have been mild a rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than occurs commonly, and heart rates below 40 beats per minute bradycardia were seen in about 2 of 100 patients. Symptoms o insufficiency, usually of the Raynaud type, have occurred in ap patients. Cardiac failure, hypotension, and rhythm/conduction di occurred in about 1 of 100 patients. Single instances of first degree a block have been reported; intensification of AV block is a known (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTION

System — Dizziness or fatigue reported in approximately 2 of 100 sedation, and change in behavior reported in approximately

Respiratory — Bronchospasm reported in approximately 1 CONTRAINDICATIONS and WARNINGS). **Gastrointestinal -** abdominal discomfort, constipation, vomiting, indigestion, an flatulence each reported in 1 to 5 of 1000 patients. **Miscellan** following reported in 1 to 5 of 1000 patients: rash; pruritus; headach skin; impotence or decreased libido; facial swelling; weight gain; s nasal stuffiness; sweating; tinnitus; blurred vision. Although relatio not clear, sleep disturbances have been reported. The oculomuc associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects rep adrenergic blocking agents have not been reported with nad considered potential adverse effects of nadolol. **Central Nervous** mental depression progressing to catatonia; visual disturbances; ha reversible syndrome characterized by disorientation for time a memory loss, emotional lability with slightly clouded sensorium; d on neuropsychometrics. **Gastrointestinal —** mesenteric arterial colitis. **Hematologic —** agranulocytosis; thrombocytopenic or r purpura. **Allergic —** fever combined with aching and sore t respiratory distress. **Miscellaneous —** reversible alopecia; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circula In addition to gastric lavage, employ the following measure determining duration of corrective therapy, take note of long durati

Excessive Bradycardia — Administer atropine (0.25 to 1. response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diureti that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent ar derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZE

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradu 80 mg increments at 3 to 7 day intervals until optimum clinical res slowing of the heart rate; usual maintenance dose is 80 to 240 m respond to 160 mg or less daily). If treatment is to be disconti gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually ir increments until optimum blood pressure reduction is achieved; us is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; dosage in these patients.

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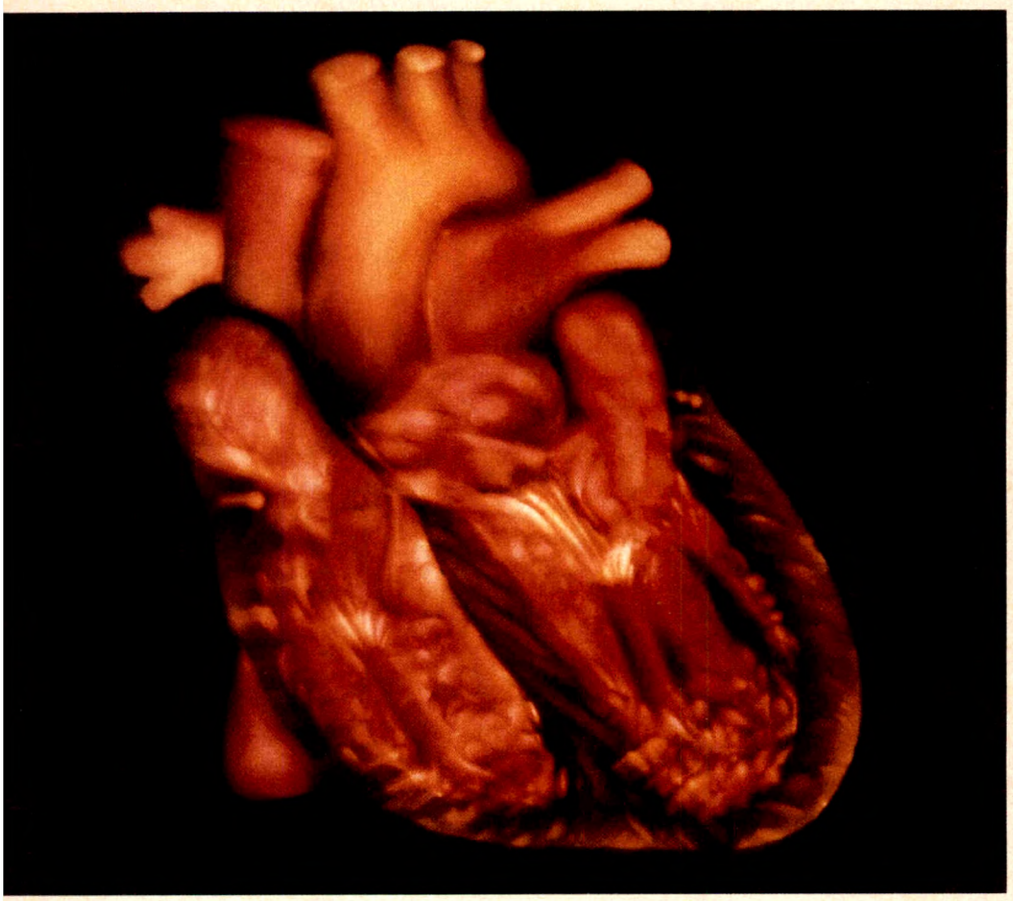

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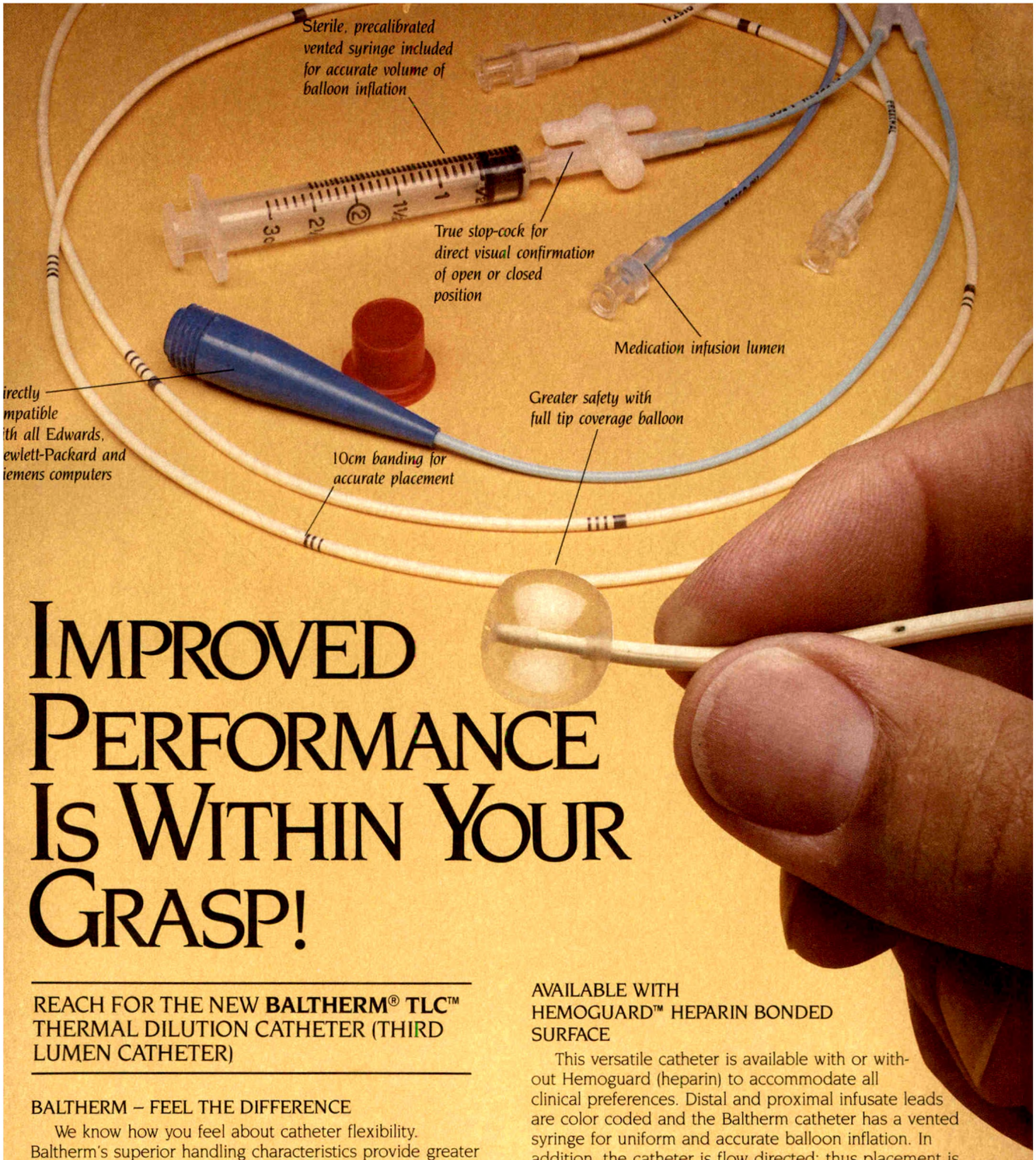

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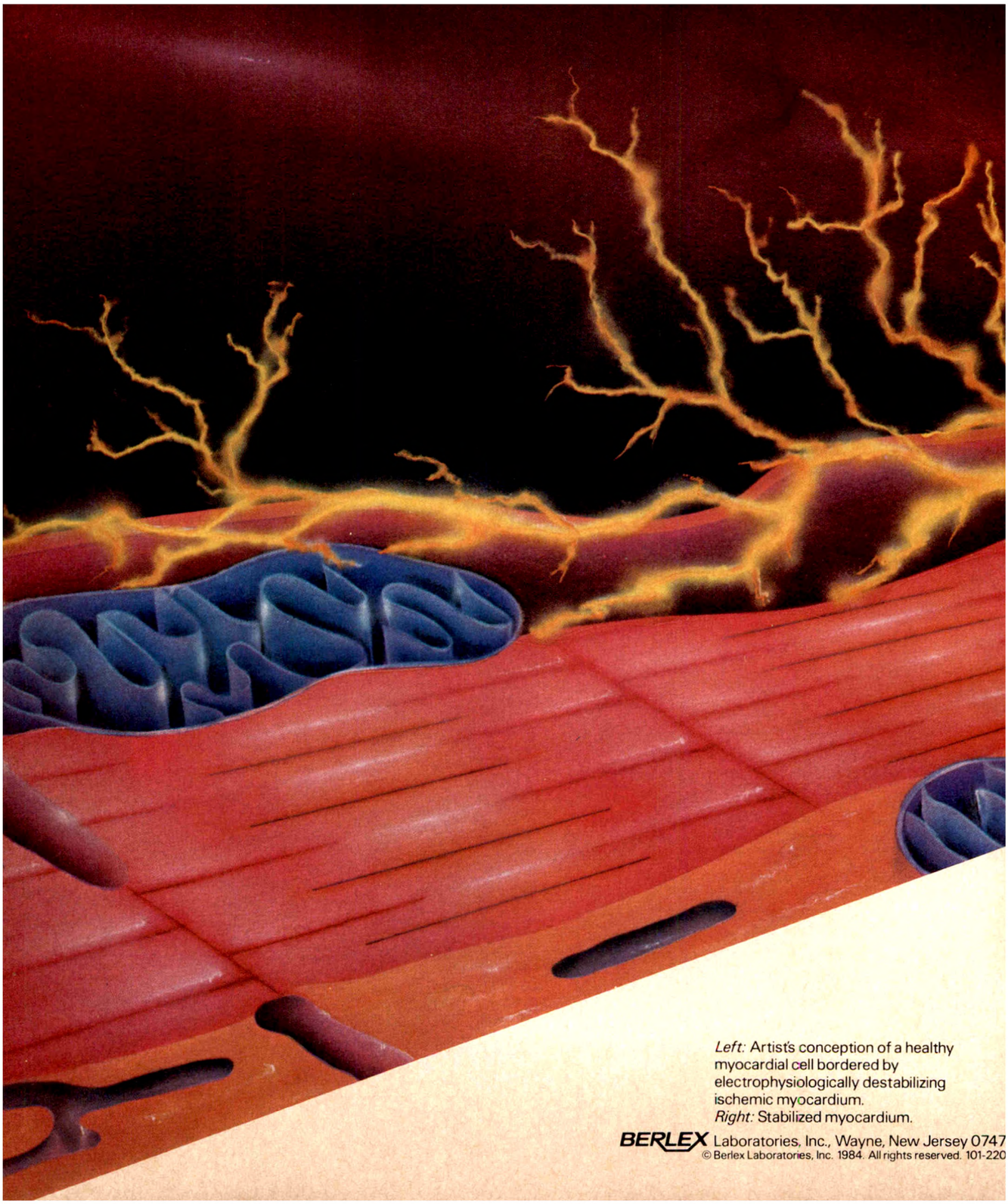

Left: Artist's conception of a healthy myocardial cell bordered by electrophysiologically destabilizing ischemic myocardium.
Right: Stabilized myocardium.

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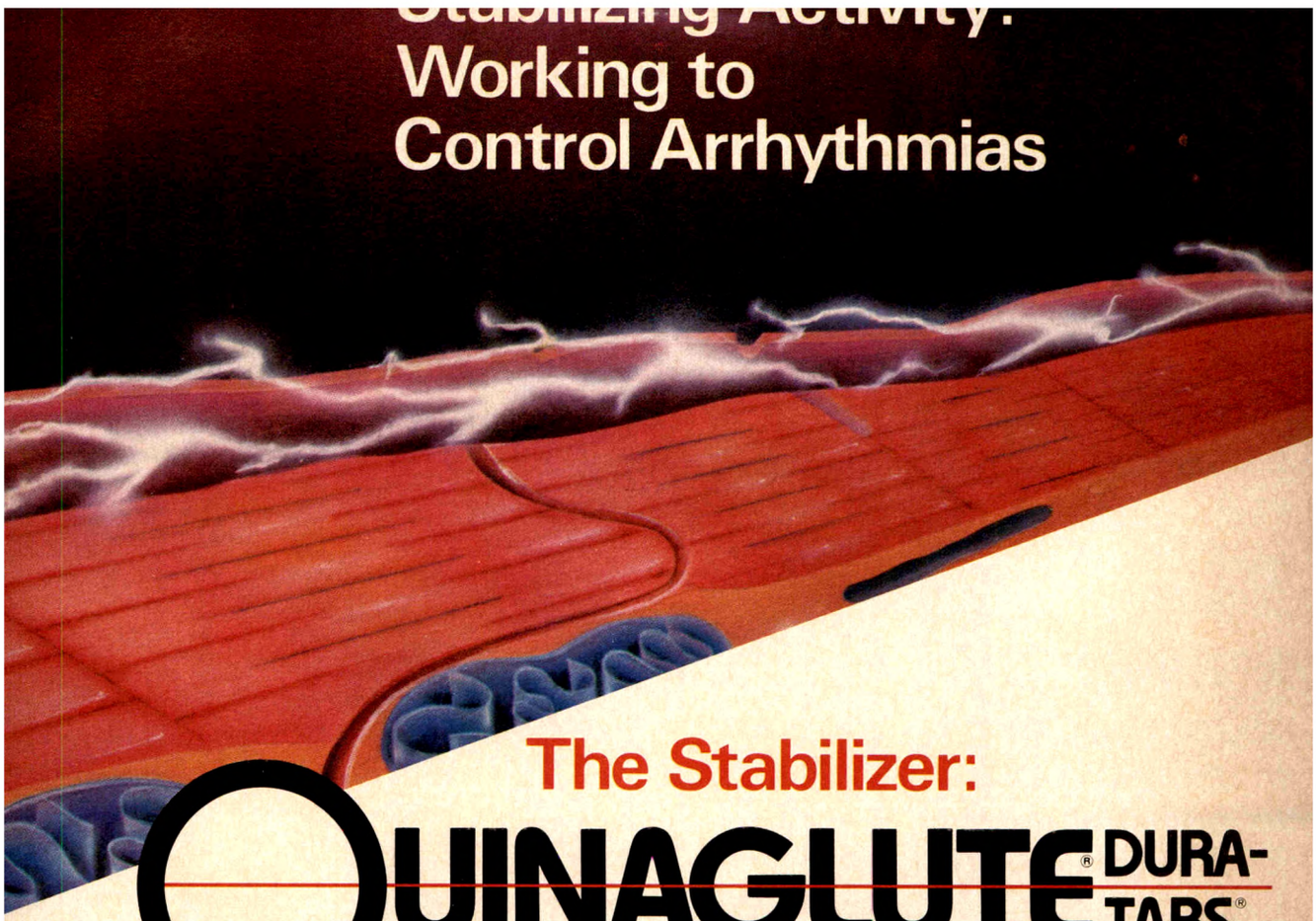

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CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.
2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.
3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.
4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.
5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.
7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.
8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.
Information for Patients: As with all solid oral medications, Quinaglute (quinidine gluconate) Dura-Tabs (sustained-release tablets) should be taken with an adequate amount of fluid, preferably in an upright position, to facilitate swallowing.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.
Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
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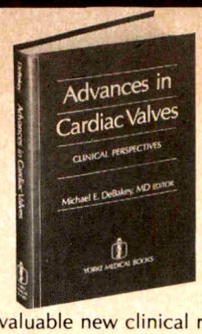

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CONTRIBUTORS INCLUDE

Mauro Abbate
Franz W. Amann
Manuel J. Antunes
Kit V. Arom
P. Barzellotti
Enrico Baruffi
Giuseppe Battaglia
Eugene M. Baudet
Marco Beneditti
Deiter Burckhardt
Jorge L. Camunas
R. Carlier
E. Stanley Crawford
Luigi C. D'Alessandro
Michael E. DeBakey
Doriano DeLuca
Phillipe Despins
Frank E. Deuvaert
Maria Diaz
P. Di Francesco
C. Doutremepuich
Henri Dupon
D. Duveau
Robert Emery
Manuel R. Estioko
F. Fabbrizzi
Rocco Gallo
Maurizio Gentile
Carl C. Gill
Filippo Giordano
Erich Gradel
Richard J. Gray
Joachum Hasse
Andreas Hoffmann
Dieter Horstkotte
Jimmy F. Howell
Roy A. Jurado
Robert B. Karp
Thomas E. Kersten
Robin H. Kinsley
Reiner Korfer
Morris N. Kotler
Gerald M. Lawrie
Jean-Louis LeClerc
William G. Lindsay
Robert S. Litwak
Alberto Lomeo
J. L. Michaud
Bruce P. Mindich
Gary S. Mintz
Orazio Monaco
George C. Morris
Angelo Moschetto
Demetre M. Nicoloff
William F. Northrup, III
F. Ortisi
Ioannis Panidis
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CORONARY HEART DISEASE

251 **Medically Directed At-Home Rehabilitation Soon After Clinically Uncomplicated Acute Myocardial Infarction: A New Model for Patient Care**

ROBERT F. DeBUSK, WILLIAM L. HASKELL, NANCY H. MILLER, KATHY BERRA, and CRAIG BARR TAYLOR, *In cooperation with* WALTER E. BERGER III *and* HENRY LEW

Medically directed at-home rehabilitation was compared with group rehabilitation that began 3 weeks after clinically uncomplicated acute myocardial infarction (AMI) in 127 men, mean age 53 ± 7 years. Between 3 and 26 weeks after AMI, adherence to individually prescribed exercise was equally high (≥71%), the increase in functional capacity equally large (1.8 ± 1.0 METs) and nonfatal reinfarction and dropout rates equally low (both ≤3%). No testing- or training-related complications occurred in either group. Medically directed at-home rehabilitation has the potential to increase the availability and to decrease the cost of rehabilitating low-risk survivors of AMI.

258 **Effect of Beta-Adrenergic Blockade on the Results of Exercise Testing Related to the Extent of Coronary Artery Disease**

STEPHEN W.-C. HO, MICHAEL J. McCOMISH, and ROGER R. TAYLOR

Maximal treadmill exercise testing was carried out in 50 patients with angiographically documented coronary artery disease in the presence and absence of β-adrenoceptor blockade. This treatment increased the duration of exercise, delayed the onset of angina or suppressed its occurrence and, hence, altered the limiting symptom, delayed the onset of ST-segment depression and reduced maximal ST depression. Inconclusive tests (absence of ST-segment changes and failure to reach target heart rate) were increased. Without β blockade, there was a significantly shorter duration of exercise in those with left main (LM) disease, and 3-vessel or LM disease were infrequent in the absence of limitation by angina, features abolished by β blockade. It is concluded that β blockade obscures the diagnostic and prognostic interpretation of exercise testing and impairs the ability to select those likely to have extensive coronary obstructive disease.

263 **Early Exercise Training in Patients Older than Age 65 Years Compared with that in Younger Patients After Acute Myocardial Infarction or Coronary Artery Bypass Grafting**

MARK A. WILLIAMS, CARL M. MARESH, DENNIS J. ESTERBROOKS, JAMES J. HARBRECHT, and MICHAEL H. SKETCH

To evaluate potential benefits that elderly cardiac patients might gain from early exercise programs, 361 cardiac patients were studied. Seventy-six patients were aged 65 years or older. All patients participated in a 12-week exercise program after an acute myocardial infarction or coronary artery bypass grafting. Comparison of data before and after exercise revealed that elderly patients had significant decrease in body weight, percent body fat, resting heart rate, submaximal average double product, and submaximal average rating of perceived exertion. Maximal achieved heart rate and METs significantly increased. Magnitudes of change seen in the elderly were similar to those seen in younger patients. These results suggest that the benefits of an early exercise program in younger patients may also be expected in elderly patients.

267 **Early Positive Exercise Test and Extensive Coronary Disease: Effect of Antianginal Therapy**

JHULAN MUKHARJI, MARK KREMERS, KIRK LIPSCOMB, and C. GUNNAR BLOMQVIST

To examine the effect of antianginal therapy on the incidence of an early positive exercise response, 57 men with stable angina pectoris underwent bicycle ergometry before and after treatment with a calcium-blocking agent and long-acting nitrates. A 63% reduction in early positive responses was noted after therapy. In 24 pa-

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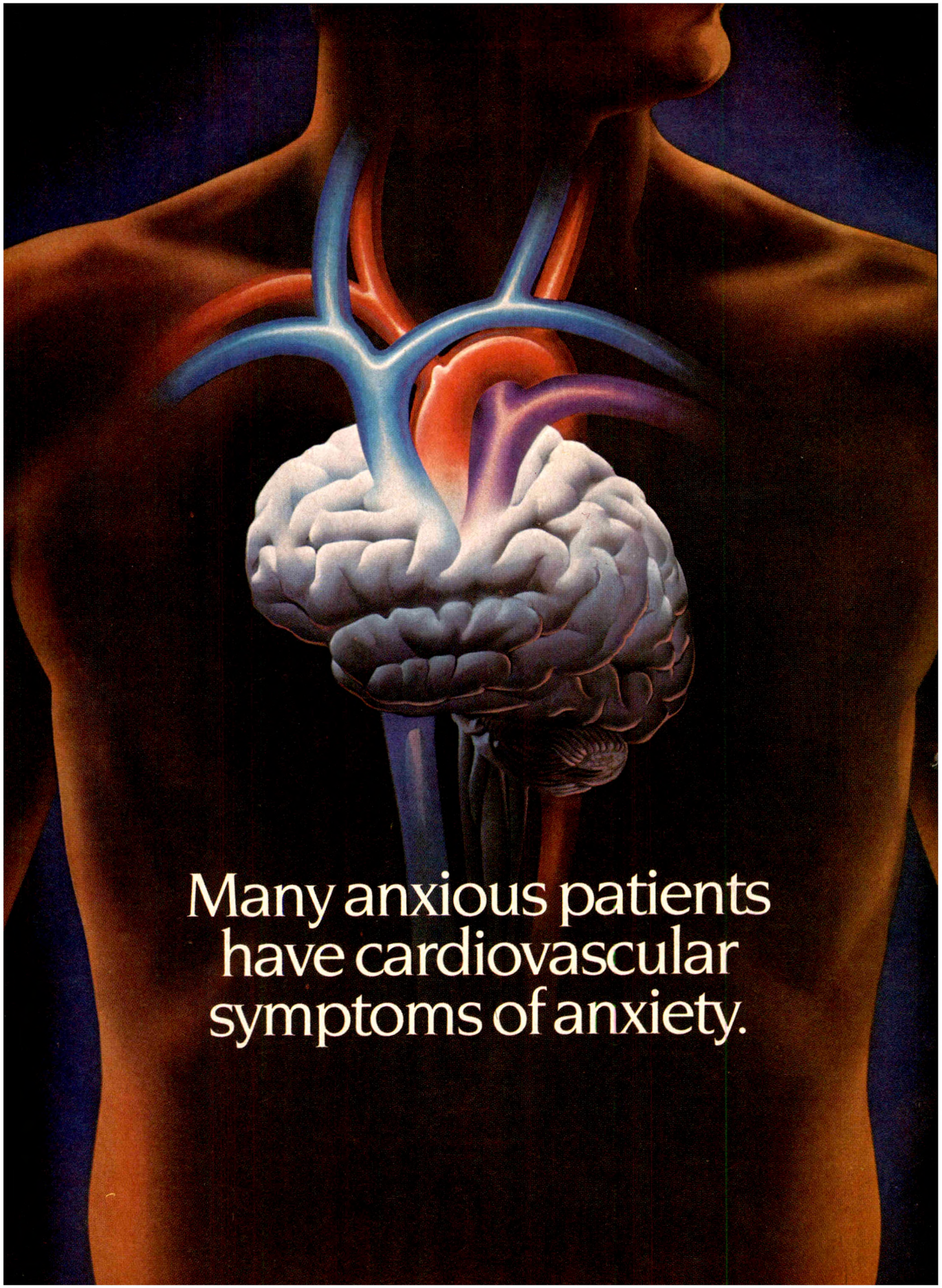
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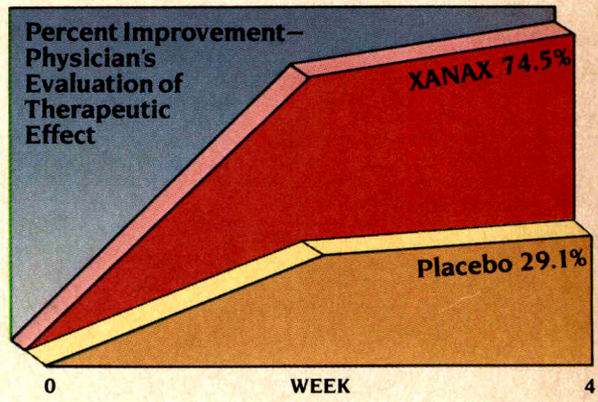

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1. Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. J *Clin Psychiatry* 1981;42:347-351.

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Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

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Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

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Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

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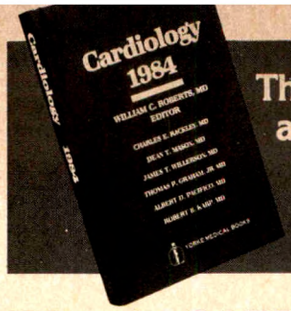

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tients who underwent coronary arteriography, the sensitivity and specificity of an early positive response in predicting 3-vessel and left main disease changed from 92% and 58% before to 42% and 75% after therapy. The positive and negative predictive values changed from 69% and 88% before to 63% and 63% after therapy. It is concluded that antianginal therapy reduces the usefulness of an early positive exercise response in screening for extensive coronary disease.

271 Improved Accuracy of the Exercise Electrocardiogram: Identification of Three-Vessel Coronary Disease in Stable Angina Pectoris by Analysis of Peak Rate-Related Changes in ST Segments

PETER M. OKIN, PAUL KLIGFIELD, OLIVIER AMEISEN, HARVEY L. GOLDBERG, and JEFFREY S. BORER

To assess the applicability of the rate-related change in ST-segment depression (ST/HR slope) for the identification of 3-vessel coronary artery disease (CAD), 50 patients in whom exercise electrocardiography and coronary cineangiography had been performed for suspected CAD were retrospectively evaluated. Standard electrocardiographic criteria ($\geq$1 mm horizontal or downsloping ST depression) identified 3-vessel CAD with a sensitivity of 78%, specificity of 56% and positive predictive value of only 50%. Peak ST/HR slope criteria ($\geq$6.0 μV/beat/min) identified 3-vessel CAD with a sensitivity of 78%, specificity of 97% and positive predictive value of 93%. Overall test accuracy using measured peak ST/HR slope was 90% compared with 64% for standard ST-depression criteria. It is concluded that analysis of the peak ST/HR slope can greatly improve the diagnostic accuracy of exercise electrocardiography, and that further prospective study of this method is indicated.

277 Effect of Coffee on Exercise-Induced Angina Pectoris Due to Coronary Artery Disease in Habitual Coffee Drinkers

KENNETH M. PITERS, ANTONIO COLOMBO, HAROLD G. OLSON, and SAMUEL M. BUTMAN

The acute effects of coffee on exercise-induced angina pectoris were studied in 17 patients with coronary artery disease using a double-blind treadmill protocol. Both 1 and 2 cups of caffeinated coffee increased the exercise duration until onset of angina (8 and 12%, respectively, $p < 0.05$), whereas 2 cups of decaffeinated coffee had no effect. The exercise duration until 0.1 mV of ST-segment depression, as well as the heart rate, blood pressure and double product at angina and at 0.1 mV of ST-segment depression were similar after ingestion of caffeinated or decaffeinated coffee. Serum caffeine levels indicated adequate absorption of caffeine. The acute ingestion of 1 to 2 cups of caffeinated coffee had no deleterious effect on exercise-induced angina in patients with coronary artery disease.

281 Propranolol-Verapamil Versus Propranolol-Nifedipine in Patients with Severe Angina Pectoris of Effort: A Randomized, Double-Blind, Crossover Study

MICHAEL D. WINNIFORD, KAY L. FULTON, JAMES R. CORBETT, CHARLES H. CROFT, and L. DAVID HILLIS

Sixteen patients with continuing angina and a positive exercise tolerance test despite therapy with propranolol were maintained on a constant dose of propranolol and, in addition, received verapamil (360 mg/day) and nifedipine (60 mg/day) for 3 weeks each in a double-blind, randomized fashion. In comparison with propranolol alone, a propranolol-verapamil combination reduced anginal frequency, nitroglycerin usage, and the magnitude of ST-segment depression during exercise, whereas a propranolol-nifedipine combination exerted no significant effect on anginal frequency or nitroglycerin usage. Thus, in patients with severe angina of effort who took propranolol alone, the addition of verapamil was more effective than the addition of nifedipine.

286 Hemodynamic and Metabolic Effects of Diltiazem During Coronary Sinus Pacing with Particular Reference to Left Ventricular Ejection Fraction

MARTIN A. JOSEPHSON, JAMES HOPKINS, and BRAMAH N. SINGH

Fifteen patients with coronary artery disease undergoing cardiac catheterization were studied before and after intravenous diltiazem, 0.165 to 0.25 mg/kg. Hemodynamic variables, metabolic measurements and left ventricular ejection fractions were obtained at rest and during coronary sinus pacing before and during diltiazem administration. At rest, systemic resistance was reduced by 22% ($p < 0.01$) and mean arterial pressure by 12% ($p < 0.01$); cardiac index increased from 2.4 $\pm$ 0.4 to 2.6 $\pm$ 0.4 liters/min/m^2 ($p < 0.01$) with no significant change in heart rate. The mean pulmonary artery pressure increased from 17 $\pm$ 2 to 19 $\pm$ 3 mm Hg ($p < 0.01$), but other hemodynamic variables were not affected. Diltiazem given during pacing reduced mean aortic pressure (112 $\pm$ 15 to 104 $\pm$ 15 mm Hg, $p < 0.05$) but other hemodynamic variables were not affected significantly. Diltiazem did not affect left ventricular ejection fraction at rest, but significantly lessened the decrease in ejection fraction (16 vs 8%, $p < 0.01$) that occurred during pacing.

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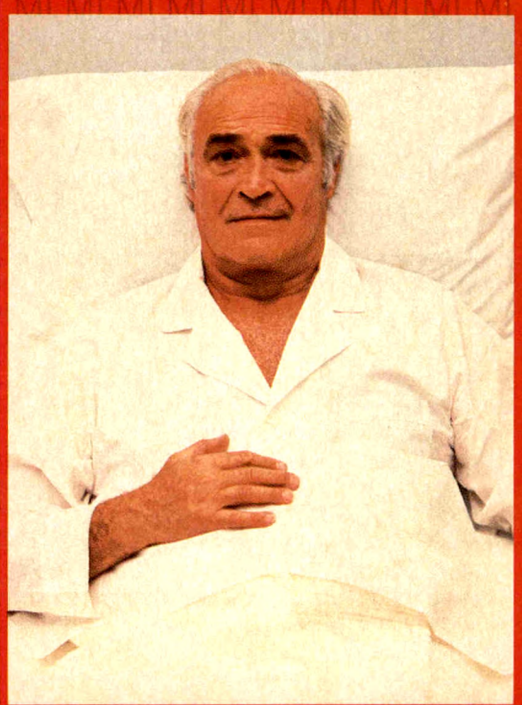

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1. The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. *304(14)*:801-807, April 2, 1981.

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Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

In patients with nonallergic bronchospasm or with a history of nonallergic bronchospasm (e.g., chronic bronchitis, emphysema), BLOCADREN should be administered with caution.

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WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal – Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm: In patients with nonallergic bronchospasm or with a history of nonallergic bronchospasm (e.g., chronic bronchitis, emphysema), BLOCADREN should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol (see OVERDOSAGE).

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: Impaired Hepatic or Renal Function: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN® (Timolol Maleate, MSD) is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported. When using these agents concomitantly, patients should be observed carefully to confirm that the desired therapeutic effect has been obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy – Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
SKIN		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure – Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema – Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.
‡Only principal reason for withdrawal in each patient is listed.
These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole:* extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive:* gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Hematologic:* nonthrombocytopenic purpura; *Endocrine:* hyperglycemia, hypoglycemia; *Skin:* rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* arthralgia; *Nervous System:* local weakness; *Psychiatric:* depression, nightmares, somnolence, insomnia, nervousness, diminished concentration, hallucinations; *Respiratory:* cough; *Special Senses:* visual disturbances, diplopia, ptosis, dry eyes; *Urogenital:* impotence, urination difficulties.

There have been reports of retroperitoneal fibrosis in patients receiving timolol maleate and in patients receiving other beta-adrenergic blocking agents. A causal relationship between this condition and therapy with beta-adrenergic blocking agents has not been established.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN® (Timolol Maleate, MSD), but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System:* reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular:* intensification of AV block (see CONTRAINDICATIONS); *Digestive:* mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* agranulocytosis, thrombocytopenic purpura; *Allergic:* erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous:* reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations. 183 (DC7117616)

MSD MERCK SHARP & DOHME

For more detailed information, consult your MSD Representative and the Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J3BL19 (616)

291 Familial Aggregation and Early Expression of Hyperapobetalipoproteinemia

ALLAN SNIDERMAN, BABIE TENG, JACQUES GENEST, KATHERINE CIANFLONE, SHOLOM WACHOLDER, and PETER KWITEROVICH Jr.

Hyperapobetalipoproteinemia is the combination of a normal or near normal low-density lipoprotein (LDL) cholesterol level in the face of an elevated LDL apoB level. This study examined the offspring of parents with premature coronary artery disease and hyperapobetalipoproteinemia. A substantial portion, that is in 3, had hyperapobetalipoproteinemia and of these only the minority had clearly elevated plasma triglyceride or LDL cholesterol levels. Thus, hyperapobetalipoproteinemia appears to be present frequently in the offspring of affected families, an observation which may explain, at least in part, the familial aggregation of coronary artery disease.

296 Continuous Positive Airway Pressure by Face Mask in Acute Cardiogenic Pulmonary Edema

JUKKA RÄSÄNEN, JUHANI HEIKKILÄ, JOHN DOWNS, PERTTI NIKKI, IRMA VAISANEN, and ANNE VIITANEN

Continuous positive airway pressure administered by face mask was compared prospectively to ambient airway pressure breathing in 40 patients with respiratory failure from acute cardiogenic pulmonary edema. The use of 10 cm H_2O continuous positive airway pressure improved gas exchange and reduced work of breathing within 10 minutes. Simultaneously, heart rate and systolic blood pressure decreased, indicating relief of the circulatory stress associated with pulmonary edema. No complications occurred with either treatment. The patients treated with an ambient airway pressure appeared to be at greater risk of requiring endotracheal intubation and ventilator treatment than those who received continuous positive airway pressure.

301 Intracoronary Thrombolytic Therapy in Acute Myocardial Infarction: A Prospective, Randomized, Controlled Trial

ALBERT E. RAIZNER, FRANCISCO A. TORTOLEDO, MARIO S. VERANI, RICHARD E. VAN REET, *with* JAMES B. YOUNG, FRANK D. RICKMAN, W. RICHARD CASHION, DAVID A. SAMUELS, CRAIG M. PRATT, MOHAMMED ATTAR, HOWARD S. RUBIN, JOHN M. LEWIS, MILTON S. KLEIN, *and* ROBERT ROBERTS

A prospective, randomized trial was designed to assess the efficacy of intracoronary thrombolytic therapy with streptokinase (STK) in acute myocardial infarction. Sixty-four patients were randomized into a traditional control group, an intracoronary STK group and a nitroglycerin group that was treated identically to the STK group except that the patients did not receive STK. Global ejection fraction (EF) by radionuclide ventriculography measured before therapy and 7 to 10 days later demonstrated wide variability of response among persons in all groups but improved significantly in the STK-recanalized patients. The greatest magnitude of improvement occurred in STK-recanalized patients whose EF was low ($\leq$45) on admission. Regional EF of the infarcting segments improved in the STK group as a whole, and more strikingly, in the STK-recanalized patients.

309 Intravenous Versus Intracoronary Streptokinase in Acute Myocardial Infarction

RUSSELL P. VALENTINE, DOUGLAS E. PITTS, JO ANN BROOKS-BRUNN, JAMES G. WILLIAMS, EUGENE VAN HOVE, and PAUL E. SCHMIDT

Sixty-six patients with acute myocardial infarction treated with intravenous (i.v.) streptokinase (STK) were compared with 98 patients treated with intracoronary (i.c.) STK in a prospective trial of coronary thrombolysis. Lysis occurred in 51% of patients who received i.v. STK and 59% of patients who received i.c. STK. A significant reduction in time from onset of pain to administration of STK occurred. Complications were identical in the 2 groups. Patients in whom reperfusion was achieved had a significantly greater ejection fraction increase than those in whom it was not. It is concluded that the safety and efficacy of i.v. and i.c. STK are equivalent, and that i.v. STK offers significant advantages in shortening time to treatment and in making lytic therapy more widely available.

313 Follow-Up After Coronary Arterial Reperfusion with Intravenous Streptokinase in Relation to Residual Myocardial Infarct Artery Narrowings

ROLF SCHRÖDER, HANS VÖHRINGER, THOMAS LINDERER, GIANCARLO BIAMINO, THOMAS BRÜGGEMANN, and ENZ-RUDIGER V. LEITNER

Quantitative measurements of the diameter stenosis after 24 hours and in the fourth week after successful intravenous thrombolysis in 15 patients revealed a significant decrease from 62 to 55%. Sixty-three patients with a patent infarct-related artery in the fourth week were followed up for a mean of 34 months. Fifty-nine percent of patients have had a stenosis less than 65%, and 41% have had a stenosis greater than 65% in diameter.

Continued on page A24

Eighteen patients underwent repeat study after 26 months (range 18 to 40). It appears that in patients with a residual stenosis less than 65% in the fourth week after successful intravenous streptokinase, reocclusion or reinfarction is a relatively rare event, whereas it is frequent in patients with a more severe residual stenosis. Percutaneous transluminal coronary angioplasty may be advisable in these latter patients.

318 Value of Radionuclide Angiography for Predicting Specific Cardiac Events After Acute Myocardial Infarction

KENNETH G. MORRIS, SEBASTIAN T. PALMERI, ROBERT M. CALIFF, RAY A. McKINNIS, MICHAEL B. HIGGINBOTHAM, R. EDWARD COLEMAN, and FREDERICK R. COBB

The value of rest and exercise radionuclide angiography (RNA) for predicting specific events including death, recurrent infarction, coronary care unit readmission for unstable chest pain and medically refractory angina after acute myocardial infarction (AMI) was studied in 106 consecutive survivors of AMI. RNA measures of left ventricular function, rest and exercise ejection fraction, were predictive of subsequent mortality, whereas the change in ejection fraction from rest to exercise, which reflects residual potentially ischemic myocardium, was predictive of subsequent ischemic events. Significant correlations were found between RNA variables and a variety of clinical descriptors previously reported to have prognostic significance. Rest and exercise RNA after AMI provides significant prognostic information regarding specific events during follow-up independent of that provided by clinical assessment.

325 Prognostic Significance of Precordial ST-Segment Depression During Inferior Acute Myocardial Infarction

MARK A. HLATKY, ROBERT M. CALIFF, KERRY L. LEE, DAVID B. PRYOR, GALEN S. WAGNER, and ROBERT A. ROSATI

The significance of precordial ST-segment depression during inferior acute myocardial infarction (AMI) is controversial. In 162 such patients it was found that those with ST depression in leads V_1 through V_3 developed significantly larger infarcts as assessed by a QRS scoring system. Hospital mortality was 4% (3 of 75 patients) among patients without ST depression, and 13% (11 of 87) in patients with ST depression. The relation between the amount of ST depression and hospital mortality remained significant ($p < 0.003$) after adjusting for other potentially prognostic factors. Among patients discharged from the hospital, the 5-year survival was 92% in those without precordial ST depression and 80% in those with precordial ST depression. Thus, precordial ST-segment depression on the admission electrocardiogram during an inferior acute myocardial infarction indicates a larger infarction, predicts a higher hospital mortality, and suggests a worse long-term prognosis after discharge.

330 Isosorbide Dinitrate Sublingual Therapy for Inferior Myocardial Infarction: Randomized Trial to Assess Infarct Size Limitation

PEDRO PABÓN OSUNA, LUIS M. GARCÍA MORENO, ANTONIO ARRIBAS JIMENEZ, ANGEL SALA, SÁNCHEZ-CASTILLO, CÁNDIDO MARTÍN LUENGO, JOSÉ SÁNCHEZ HERNÁNDEZ, LUIS CASTAÑO BAZO, MANUEL CASCON BUENO, MAXIMILIANO DIEGO DOMINGUEZ, and CLAUDIO LESDESMA GARCÍA

To evaluate whether sublingual isosorbide dinitrate can reduce infarct size, 41 patients with acute myocardial infarction were randomized to control ($n = 20$) and treatment ($n = 21$) groups. Patients in the treatment group received 10 mg of isosorbide dinitrate every 2 hours. Infarct size was estimated by QRS scoring, peak creatine kinase (CK) blood levels and CK curves. There was no significant difference between the groups in maximal or cumulative CK levels or QRS score (16.5% of left ventricle infarcted in the control group and 17% in the treatment group). In both groups the QRS score increased significantly at 13 hours after MI, and the increase was highly significant at 19 to 23 hours. Thus, sublingual isosorbide dinitrate did not reduce infarct size in patients with inferior myocardial infarction.

335 Frequency of Pericardial Effusion as Determined by M-Mode Echocardiography in Acute Myocardial Infarction

KERRY KAPLAN, RICHARD DAVISON, MICHELE PARKER, JEAN PRZYBYLEK, AMY LIGHT, DENNIS BRESNAHAN, HILLEL RIBNER, and JAMES V. TALANO

A pericardial friction rub occurs in 6 to 16% of patients after acute myocardial infarction (AMI), but the incidence of pericardial effusion (PE) is unknown. M-mode echocardiography was done 1, 3 and 5 days after AMI in 43 consecutive patients admitted within 24 hours of an AMI, and PE was detected in 16 (37%). The size of the PE was small in 7, moderate in 6 and large in 3. A pericardial friction rub developed in 8 (19%) of whom only 4 had PE. Pleuritic chest pain diminished by sitting up and relieved by anti-inflammatory agents developed in 12 (28%), of

Continued on page A31

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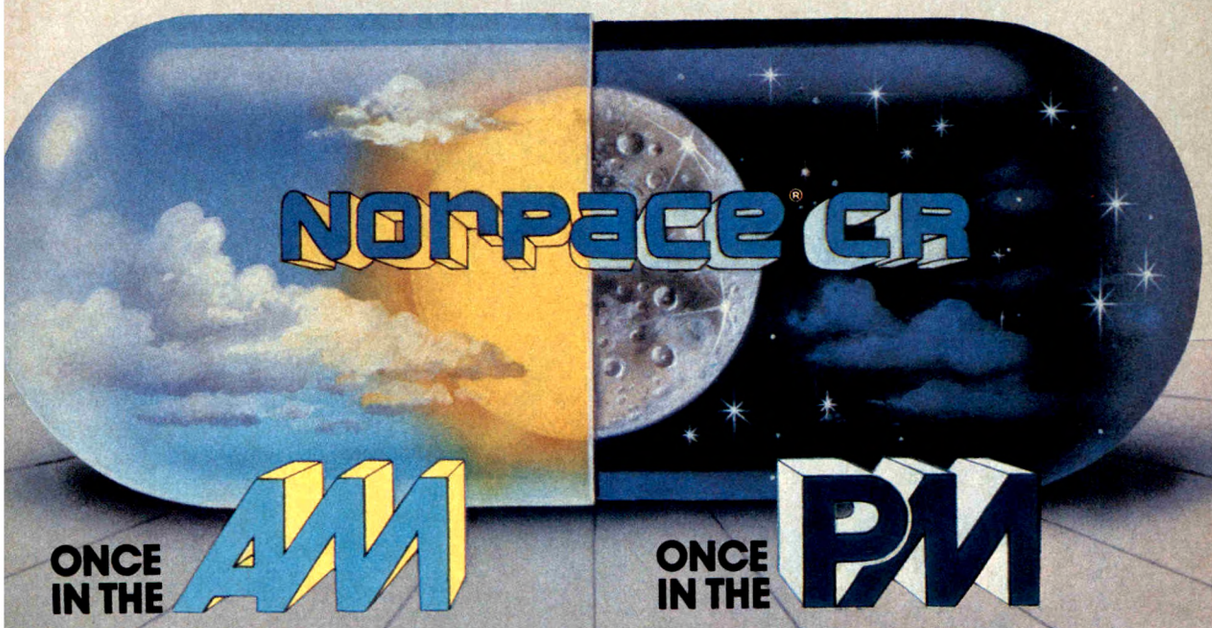

PREDICTABILITY IN A B.I.D. DOSAGE

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Please see next page for a brief summary of the complete prescribing information.

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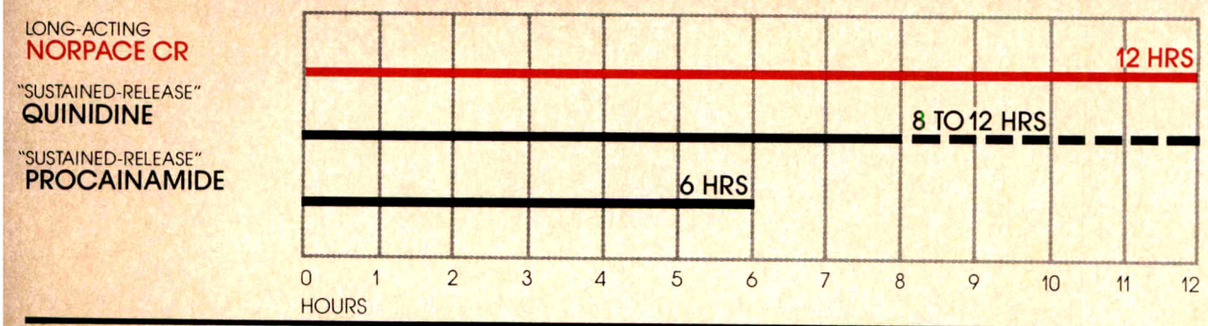
PREDICTABILITY IN A B.I.D. DOSAGE

DURATION OF ANTIARRHYTHMIC ACTION



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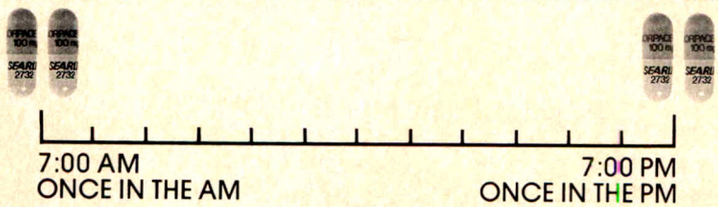

Brief Summary

Before prescribing, please consult current complete prescribing information, a summary of which follows: **Indications:** For suppression and prevention of recurrence of the following cardiac arrhythmias: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Norpace CR should not be used initially if rapid establishment of disopyramide plasma levels is desired. Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace or Norpace CR should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patients should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Therefore, a loading dose of Norpace should not be given to such patients, and initial dosage and subsequent dosage adjustments should be made under close supervision. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Concomitant administration of disopyramide phosphate with phenytoin or other hepatic enzyme inducers may cause lower disopyramide plasma levels. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention especially in males with benign prostatic hypertrophy, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

Revised 10/84 • 4J64V

4J68T

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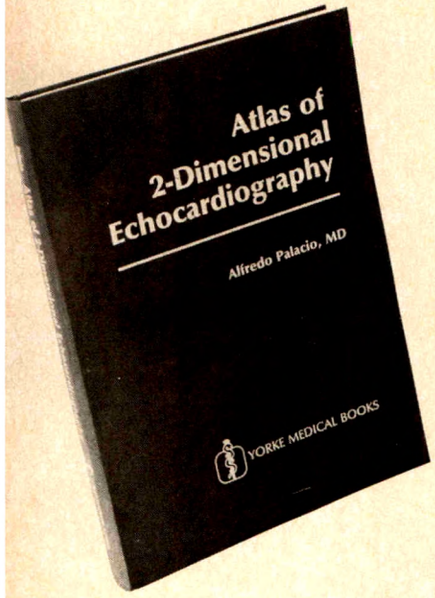

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Visken® (pindolol)

5-mg and 10-mg Tablets

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE
Visken® (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/ kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

	Total (Volunteered and Elicited)		
Body System/ Adverse Reaction	Visken (pindolol) (N = 322) %	Active controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

* Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

More than 7 million patient-years of experience

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and non-thrombocytopenic purpura.

Gastrointenstinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥ 80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 5 mg b.i.d. alone or in combination with other antihypertensive agents. An antihypertensive response usually occurs within the first week of treatment. Maximal response, however, may take as long as or occasionally longer than two weeks. If a satisfactory reduction in blood pressure does not occur within 3-4 weeks, the dose may be adjusted in increments of 10 mg per day at these intervals up to a maximum of 60 mg per day.

HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05).

[VIS-Z3 6/15/83]

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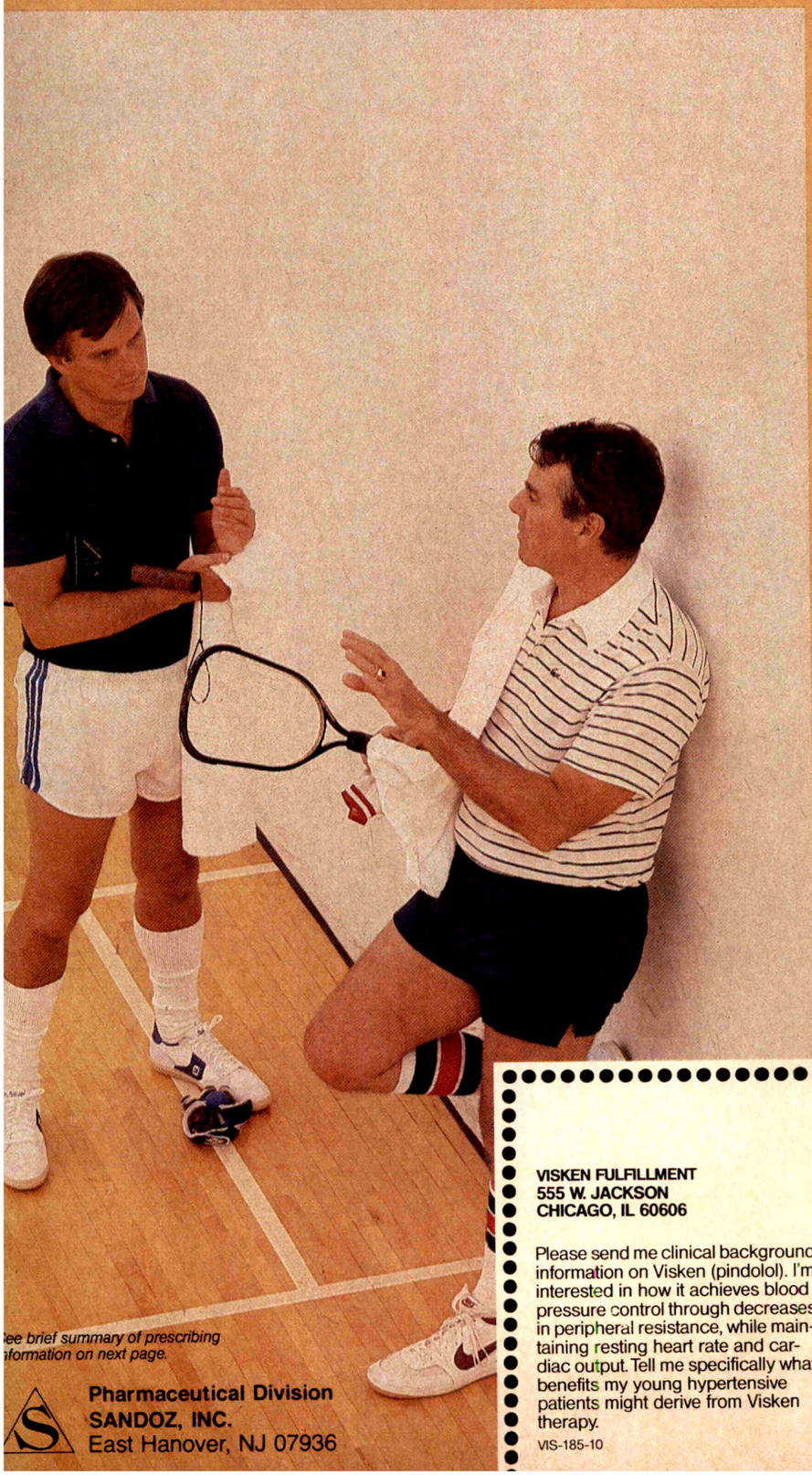
Visken®
(pindolol)
A different kind of beta blocker

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

"Would you explain the I.S.A. concept to me?"



"The intrinsic sympathomimetic activity of Visken® (pindolol) relates to its dual action on beta receptors, resulting in both blocking and stimulating effects."

When you're asked about Visken therapy, you'll want to have the answers.

See brief summary of prescribing information on next page.

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

VISKEN FULFILLMENT
555 W. JACKSON
CHICAGO, IL 60606

Please send me clinical background information on Visken (pindolol). I'm interested in how it achieves blood pressure control through decreases in peripheral resistance, while maintaining resting heart rate and cardiac output. Tell me specifically what benefits my young hypertensive patients might derive from Visken therapy.

VIS-185-10

Visken®
(pindolol) 5-mg and 10-mg Tablets

Send me the answers.

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(please print)

Address _____

City _____ State _____ ZIP _____

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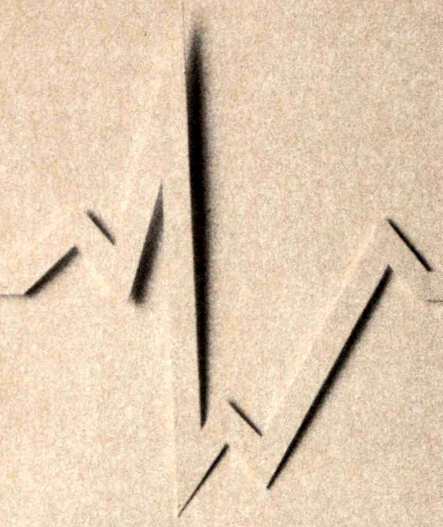

SILENT MYOCARDIAL ISCHEMIA:
Detection and Treatment

Seven eminent investigators will meet to compare perspectives on silent or asymptomatic myocardial ischemia. The symposium will be followed by a round table discussion.

Moderator

WILLIAM PARMLEY, M.D.
Professor of Medicine
Chief, Cardiovascular Division
Moffitt Hospital
University of California
San Francisco, California

"Silent Myocardial Ischemia: Classification, Prevalence, Prognosis"

PETER F. COHN, M.D.
Professor of Medicine
Chief, Cardiology Division
State University of New York Health Sciences Center
Stony Brook, New York

"The Pathophysiologic Mechanisms of Silent Ischemia"

ATTILIO MASERI, M.D., F.R.C.P., F.A.C.C.
Sir John Michael Professor of Cardiovascular Medicine
University of London;
Director, Cardiovascular Research Unit
Royal Postgraduate Medical School
Hammersmith Hospital
London, England

"Clinical Evaluation of Silent Myocardial Ischemia During Daily Life"

JOHN E. DEANFIELD, M.R.C.P.
Consultant in Cardiology
Senior Lecturer
Department of Cardiology
Hospital for Sick Children
London, England

"The Character and Cause of Transient Ischemia In and Out of Hospital"

ANDREW SELWYN, M.D.
Associate Professor of Medicine
Division of Cardiology
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

"Comparison of the Mechanisms of Silent Myocardial Ischemia and Mixed Angina: A Pathophysiologic Correlate?"

ALAN MILLER, M.D.
Chief, Cardiology Division
University Hospital
Jacksonville, Florida

"Silent Myocardial Ischemia: A Review of Therapeutic Implications"

LEON RESNEKOV, M.D., F.R.C.P.
Frederick H. Rawson Professor of Medicine
Department of Medicine-Cardiology
University of Chicago Pritzker School of Medicine
Chicago, Illinois

Date: Saturday, March 9, 1985
Time: 5:30 PM-9:00 PM
Place: California Pavilion
C&D Anaheim Hilton and Towers 777 Convention Way
Anaheim, California 92802

A reception will be held prior to the symposium, at 4:00 PM, in the California Pavilion A&B.

This symposium is sponsored by the University of Chicago School of Medicine with an educational grant provided by Pfizer Laboratories.

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Pfizer LABORATORIES DIVISION
PFIZER INC.

whom only 5 had PE. In conclusion, PE as detected by M-mode echocardiography is frequently present after AMI; and its presence is not closely associated with the occurrence of a pericardial friction rub or typical pericardial pain.

338 Contractile Properties of the Left Ventricle with an Aneurysm

STEPHEN ARVAN and PEDRO BADILLO

Percent fractional shortening properties of the left ventricle were analyzed by 2-dimensional echocardiography in 25 subjects who sustained their first anterior wall acute myocardial infarction. In 8 of the 25 subjects a left ventricular (LV) aneurysm subsequently developed. The percent fractional shortening of the basal and mid-LV segments was significantly better in group I subjects than in group II subjects. Infarct size as determined by peak creatinine kinase isoenzyme levels was large in both groups and were not significantly different from each other. Severe asynergy of the infarcted myocardium was more common in the group of patients with LV aneurysm. These results indicate that LV aneurysm formation depends upon a critical imbalance of myocardial forces where strong LV segmental contractility causes bulging of weakened ones.

342 Assessment of Hemodynamic Significance of Isolated Stenoses of the Left Anterior Descending Coronary Artery Using Thallium-201 Myocardial Scintigraphy

VICTOR KALFF, MICHAEL J. KELLY, ALAN SOWARD, RICHARD W. HARPER, PHILIP J. CURRIE, YEAN L. LIM, and AUBREY PITT

In 22 patients with isolated single-vessel left anterior descending coronary artery stenoses who were undergoing percutaneous transluminal coronary angioplasty, the results of exercise thallium-201 myocardial perfusion scintigraphy were independently predictive of the mean transstenotic pressure gradient ($p < 0.003$) after taking into account the assessment provided by coronary angiography. It is suggested that this additional information may be of most value when a coronary stenosis is less than 90% luminal diameter narrowing and its clinical significance is uncertain.

347 Clinical, Angiographic, Hemodynamic, Perfusional and Functional Changes after One-Vessel Left Anterior Descending Coronary Angioplasty

ROBERT D. OKADA, YEAN L. LIM, CHARLES A. BOUCHER, GERALD M. POHOST, DAVID A. CHESLER, and PETER C. BLOCK

Percutaneous transluminal coronary angioplasty (PTCA) was successfully performed in 20 patients with 1-vessel left anterior descending coronary artery disease. Peak workload, heart rate and systolic blood pressure all increased significantly after PTCA. Of 12 patients with an abnormal exercise electrocardiogram before PTCA, 8 had normal electrocardiograms after the procedure. Significant improvement in thallium activity was present in the anterior and septal segments of the left ventricle 1 week after PTCA. In addition, there was a significant reduction in the amount of thallium redistribution between initial and delayed images and improvements in the clearance rates from these same regions. Exercise ejection fraction response and septal wall motion also improved after PTCA. Thus, improvement in clinical, angiographic and hemodynamic factors, as well as in global and regional myocardial perfusion and function occur after PTCA.

357 Early Detection of Restenosis After Successful Percutaneous Transluminal Coronary Angioplasty by Exercise-Redistribution Thallium Scintigraphy

WILLIAM WIJNS, PATRICK W. SERRUYS, JOHAN H.C. REIBER, PIM J. de FEYTER, MARCEL van den BRAND, MAARTEN L. SIMOONS, and PAUL G. HUGENHOLTZ, *with the statistical assistance of* JAN G.P. TIJSSEN

Exercise-induced ischemia as evidenced from early and late (4 hours) postexercise thallium scintigraphy was observed in 35 of 89 asymptomatic patients 4 weeks after a primary successful percutaneous transluminal coronary angioplasty. All patients had a clinical follow-up and a control coronary angiogram a median of 6 months later. The findings of an initially abnormal scintigram was associated with a high incidence of restenosis at late angiography (positive predictive value 74%). This suggests that restenosis had already occurred to some extent at 4 weeks in most patients in whom it was going to occur.

362 **Comparison of Preoperative, Operative and Postoperative Variables in Asymptomatic or Minimally Symptomatic Patients to Severely Symptomatic Patients Three Years After Coronary Artery Bypass Grafting: Analysis of 423 Patients**

PIM J. de FEYTER, PATRICK W. SERRUYS, RONALD W. BROWER, MARCEL van den BRAND, HARALD J. ten KATEN, PAUL G. HUGENHOLTZ, and EGBERT BOS

During a 3-year follow-up of 423 patients who underwent coronary artery bypass graft surgery, the incidence of patients in New York Heart Association class III to IV was 19%. This adverse outcome could not be predicted from 80 clinical, angiographic and perioperative variables, but was associated with a high attrition rate of the grafts. The reoperability rate was 54%. Of the patients in whom reoperation could not be performed, half of them improved to class I to II with intensive medical treatment. The reoperable patients were initially offered an intense medical treatment, which resulted in an improvement to class I to II in one-third of the patients. The nonresponders underwent reoperation after which the majority improved to class I to II.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

367 **Usefulness of Electrophysiologic Testing in Evaluation of Amiodarone Therapy for Sustained Ventricular Tachyarrhythmias Associated with Coronary Heart Disease**

LEONARD N. HOROWITZ, ALLAN M. GREENSPAN, SCOTT R. SPIELMAN, CHARLES R. WEBB, JOEL MORGANROTH, HESCHI ROTMENSCH, NEIL M. SOKOLOFF, ALAN P. RAE, BERNARD L. SEGAL, and HAROLD R. KAY

The clinical value of electrophysiologic testing of amiodarone was assessed in a prospective study of 100 consecutive patients with sustained ventricular tachyarrhythmias treated with amiodarone. In 20 patients in whom ventricular tachycardia could no longer be initiated after amiodarone therapy there were no recurrences of arrhythmia. In patients in whom ventricular tachycardia remained inducible there were recurrences in 38 of 80 patients (48%). The severity of the recurrence was predicted by electrophysiologic testing. This study suggests that electrophysiologic testing is useful in the clinical management of patients with ventricular tachyarrhythmias treated with amiodarone.

372 **Cardiac Arrest and Sudden Death in Patients Treated with Amiodarone for Sustained Ventricular Tachycardia or Ventricular Fibrillation: Risk Stratification Based on Clinical Variables**

LORENZO A. DICARLO Jr., FRED MORADY, MARY JANE SAUVE, PATRICIA MALONE, JESSE C. DAVIS, THOMAS EVANS-BELL, STUART A. WINSTON, and MELVIN M. SCHEINMAN

Multivariate analysis of 11 clinical variables was performed in 104 patients with sustained, symptomatic ventricular tachycardia (VT) or ventricular fibrillation treated with amiodarone. Twenty-five patients (24%) had cardiac arrest or sudden death after 7.3 ± 6.2 (mean ± standard deviation) months of therapy. Multivariate analysis identified an ejection fraction less than 0.40, syncope or cardiac arrest before amiodarone therapy, and VT (3 or more consecutive ventricular premature depolarizations) during predischarge ambulatory electrocardiographic monitoring as variables associated with a high risk of subsequent cardiac arrest or sudden death ($p < 0.03$). Patients who had these 3 clinical variables had a much higher incidence of cardiac arrest or sudden death at 6 months (62%) and 12 months (76%) than did patients with an ejection fraction of 0.40 or greater, without syncope or cardiac arrest before amiodarone therapy, and without VT during predischarge ambulatory electrocardiographic monitoring (2% and 5%, respectively, $p < 0.02$). Risk stratification using clinical variables can predict which patients are at high risk of cardiac arrest or sudden death during amiodarone therapy.

375 **Results of Late Programmed Electrical Stimulation and Long-Term Electrophysiologic Effects of Amiodarone Therapy in Patients with Refractory Ventricular Tachycardia**

ENRICO P. VELTRI, PHILIP R. REID, EDWARD V. PLATIA, and LAWRENCE S.C. GRIFFITH

Thirteen patients with recurrent sustained ventricular tachycardia (VT) were treated with amiodarone. At control electrophysiologic study, programmed electrical stimulation (PES) induced VT in all patients: sustained VT in 11 and nonsustained VT in 2 (9 beats and 31 beats). PES at 6 ± 1.6 months (mean ± standard error) of amiodarone therapy revealed inducible VT in 12 of 13 patients: sustained VT in 11 and nonsustained VT in 1 patient (32 beats); only 1 patient with inducible VT at control study had VT suppressed at late study. At 24 ± 2 months of follow-up, 8 patients (62%) (all with inducible VT at late PES) were free of clinical arrhythmic events (syncope, sudden death), compared with 5 patients (38%) (4 with inducible VT at late PES) with events. There were no significant differences in VT cycle length, VT cycle length change, ease of inducibility or hemodynamic response to induced VT at late PES in patients with and without arrhythmic events. Thus, in patients receiving long-term ami-

Continued on page A37

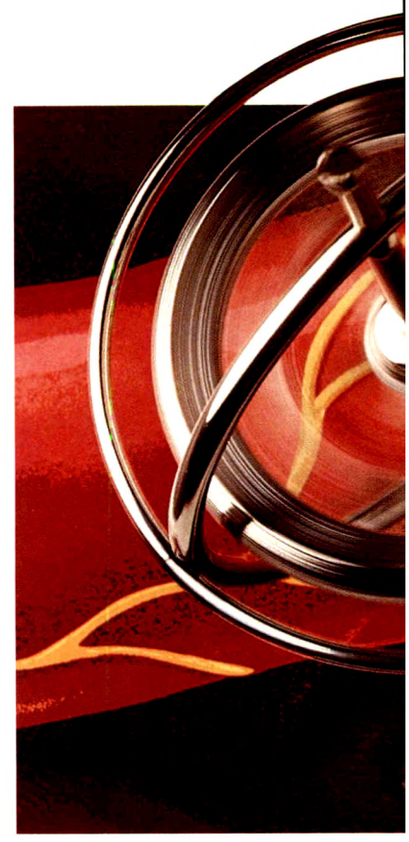
BALANCED CALCIUM CHANNEL BLOCKADE

CARDIZEM®
(diltiazem HCl)

A balance of poten with a low incid

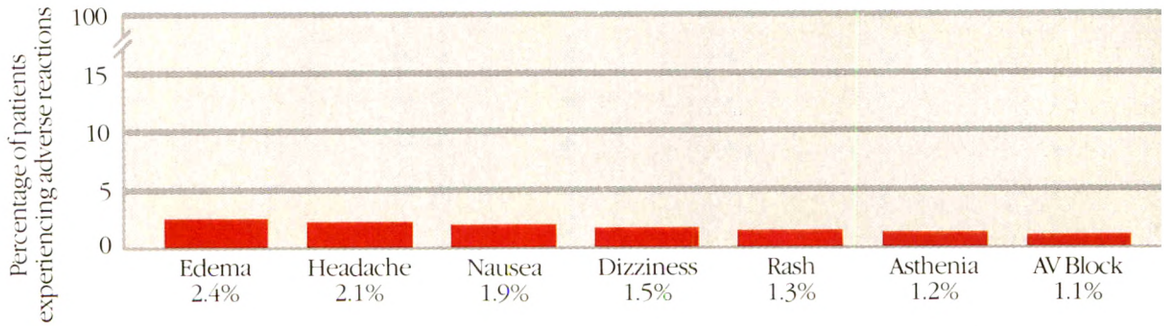
In the treatment of angina pectoris, calcium channel blockers have been found to be potent coronary vasodilators. And, due to its balanced hemodynamic profile, CARDIZEM® (diltiazem HCl) produces a low incidence of side effects, thus contributing to the patient's sense of well-being.

"The lack of significant adverse effects with diltiazem appears to correlate with the high rate of acceptance of the drug by patients and the drug's safety in both short- and long-term use."[1]



Low incidence of side effects

The adverse reactions reported most frequently with Cardizem have been:

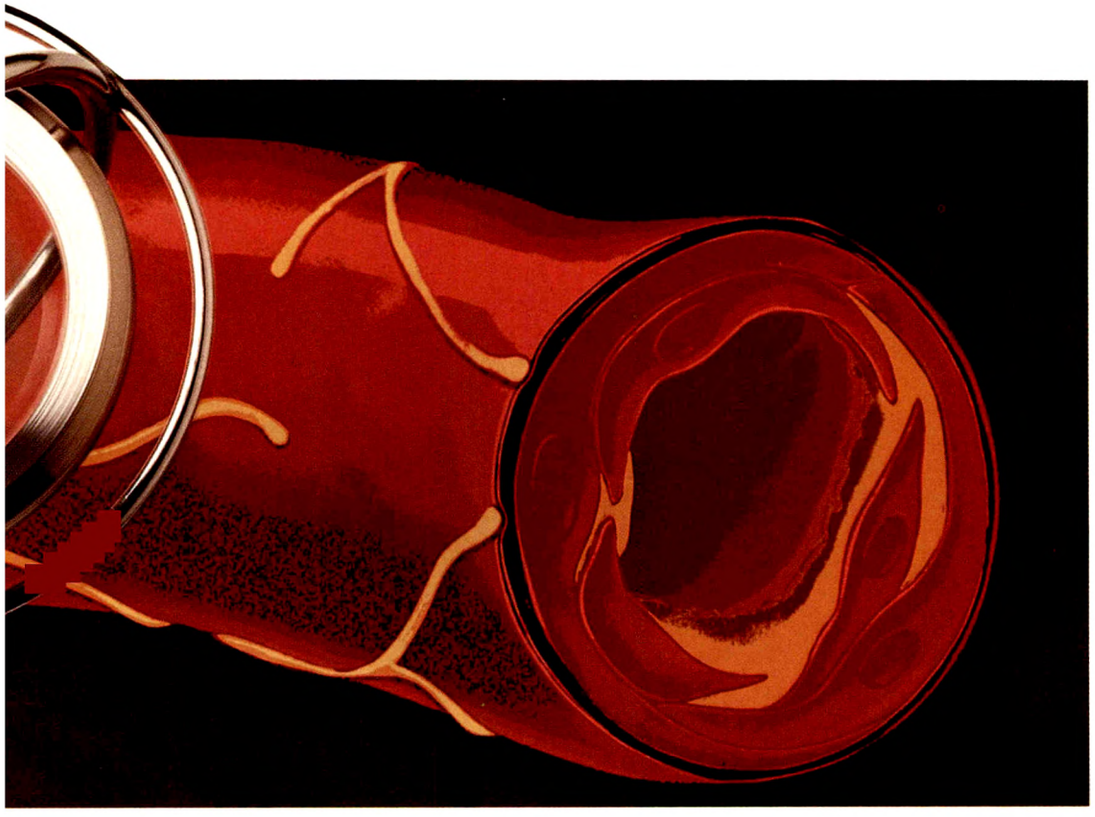


In many cases, the relationship to Cardizem has not been established.

In placebo-controlled US trials, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therap

For other adverse reactions infrequently report (<1.0%), see full prescribing information on last pag of this ad.

ɔı onary vasodilation
cɛ of side effects



Increases exercise tolerance*

CARDIZEM® (diltiazem
ɔl) allows patients to signifi-
ntly prolong exercise tolerance
en in demanding Bruce proto-
l exercise tests.[2] In time to
ıset of pain, control patients
eraged 8.0 minutes; Cardizem
ıtients averaged 9.8 minutes.

Reduces angina attack frequency*

42% to 46% decrease in effort angina attacks reported in multicenter study.[3]

CARDIZEM®
(diltiazem HCl)

The balanced calcium channel blocker

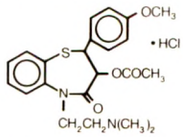
lizem is indicated in the treatment of chronic stable
ına (classic effort-associated angina) and angina due to
ɔnary artery spasm.

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studi which can be at least reasonably associated with the pharmacology calcium influx inhibition. In many cases, the relationship to CARDIZE has not been established. The most common occurrences, as well their frequency of presentation, are: edema (2.4%), headache (2.1% nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), block (1.1%). In addition, the following events were reported infrequen (less than 1%) with the order of presentation corresponding to t relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradyca dia, palpitations, congestive heart failu syncope.
Nervous System:	Paresthesia, nervousness, somnolenc tremor, insomnia, hallucinations, and amnes
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomitir mild elevations of alkaline phosphatase, SG SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivi
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vas spastic angina developed periods of transient asymptomatic asyst approximately five hours after receiving a single 60-mg dose CARDIZEM.

The following postmarketing events have been reported inf quently in patients receiving CARDIZEM: erythema multiforme; le kopenia; and extreme elevations of alkaline phosphatase, SG SGPT, LDH, and CPK. However, a definitive cause and effect betwe these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Sin oral doses of 300 mg of CARDIZEM have been well tolerated healthy volunteers. In the event of overdosage or exaggerated sponse, appropriate supportive measures should be employed addition to gastric lavage. The following measures may be considere

Bradycardia	Administer atropine (0.60 to 1.0 mg). If the is no response to vagal blockade, administ isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed hig degree AV block should be treated with c diac pacing.
Cardiac Failure	Administer inotropic agents (isoproteren dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterer bitartrate).

Actual treatment and dosage should depend on the severity of t clinical situation and the judgment and experience of the treati physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg a from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in the species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs considered to be in excess of 50 mg/kg, while lethality was seen monkeys at 360 mg/kg. The toxic dose in man is not known, but blo levels in excess of 800 ng/ml have not been associated with toxici

DOSAGE AND ADMINSTRATION

Exertional Angina Pectoris Due to Atherosclerotic Cor nary Artery Disease or Angina Pectoris at Rest Due to Cor nary Artery Spasm. Dosage must be adjusted to each patier needs. Starting with 30 mg four times daily, before meals and bedtime, dosage should be increased gradually (given in divid doses three or four times daily) at one- to two-day intervals ur optimum response is obtained. Although individual patients m respond to any dosage level, the average optimum dosage ran appears to be 180 to 240 mg/day. There are no available d concerning dosage requirements in patients with impaired renal hepatic function. If the drug must be used in such patients, titrati should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acu anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safe coadministered with short- and long-acting nitrates, but the have been no controlled studies to evaluate the antiangir effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NI 0088-1771-47) and in Unit Dose Identification Paks of 100 (NI 0088-1771-49). Each green tablet is engraved with MARION on o side and 1771 engraved on the other. CARDIZEM 60-mg scor tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in U Dose Identification Paks of 100 (NDC 0088-1772-49). Each yell tablet is engraved with MARION on one side and 1772 on the othe

Issued 4/1/

References:

1. Schroeder JS, Lamb IH, Ginsburg R, et al: Diltiazem for long-te therapy of coronary arterial spasm. Am J Cardiol 49:533-5 1982.
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odarone treatment, late PES does not predict clinical efficacy, the frequency of conversion from inducible VT to noninducible is low, and despite ventricular electrical instability as judged by late PES testing, amiodarone is clinically effective in high-risk patients.

380 Comparison in the Same Patient of Two Programmed Ventricular Stimulation Protocols to Induce Ventricular Tachycardia

PEDRO BRUGADA and HEIN J.J. WELLENS

Twenty-four consecutive patients with ventricular tachycardia (VT) (22 patients) or fibrillation (2 patients) were prospectively studied to compare results of 2 different programmed ventricular stimulation protocols to initiate VT. Both protocol 1 and protocol 2 started by pacing at the right ventricular (RV) apex at 100 beats/min using twice threshold current strength and up to 2 ventricular premature complexes (VPC). This initial step had a sensitivity of 25%. In protocol 1 the pacing site was, thereafter, changed to the RV outflow tract and finally the current strength was increased to 20 mA. In protocol 2 neither current strength nor pacing site were varied, but the pacing rate was increased to 120 and 140 beats/min. Thereafter the number of VPCs was increased to 3 during sinus rhythm and ventricular pacing. Protocol 1 had a sensitivity of 54% and protocol 2 a sensitivity of 83% ($p < 0.05$). Sensitivity of protocol 1 and protocol 2 in patients with VT and old myocardial infarction was 66 and 93%, respectively. When results after administration of isoproterenol were added to results of protocol 2, the sensitivity was 95% for the whole patient population, and 100% for patients with healed myocardial infarction. These observations have important implications for the design of the most successful order of programmed ventricular stimulation. Once stimulation at the RV apex using a current strength of twice threshold, a pacing rate of 100 beats/min and a maximum of 2 VPCs has failed to initiate VT, an increase in the pacing rate to 120 and 140 beats/min, and number of VPCs to 3 during sinus rhythm and ventricular pacing is a more effective means of initiating VT than changing pacing site or increasing current strength to 20 mA.

384 Late Potentials in Normal Subjects and in Patients with Ventricular Tachycardia Unrelated to Myocardial Infarction

HUMBERTO COTO, CLAUDIO MALDONADO, PRASAD PALAKURTHY, and NANCY C. FLOWERS

In this study, 50 normal athletes or athletically active subjects were evaluated for late potentials. Three normal men had late potentials indistinguishable by present analytic techniques from those encountered in postinfarction patients in whom ventricular tachycardia developed. The other 47 were recognized as normal by the absence of such markers. Of 24 patients referred for disturbances of rhythm or conduction, 11 had ventricular tachycardia and were considered in the study. Only 2 had had a myocardial infarction in the remote past. Although group differences could be demonstrated, late potentials were not found to be an impressive marker of the patient with ventricular tachycardia. Thus, the absence of late potentials was an effective marker of normal subjects, but the presence of late potentials was not an effective marker in identifying non-infarct-related, nonsustained ventricular tachycardia patients.

391 Ventricular Arrhythmia Induced by Programmed Ventricular Stimulation After Acute Myocardial Infarction

PIETRO SANTARELLI, FULVIO BELLOCCI, FRANCESCO LOPERFIDO, MARIO MAZZARI, ROCCO MONGIARDO, ANNIBALE S. MONTENERO, UGO MANZOLI, and PABLO DENES

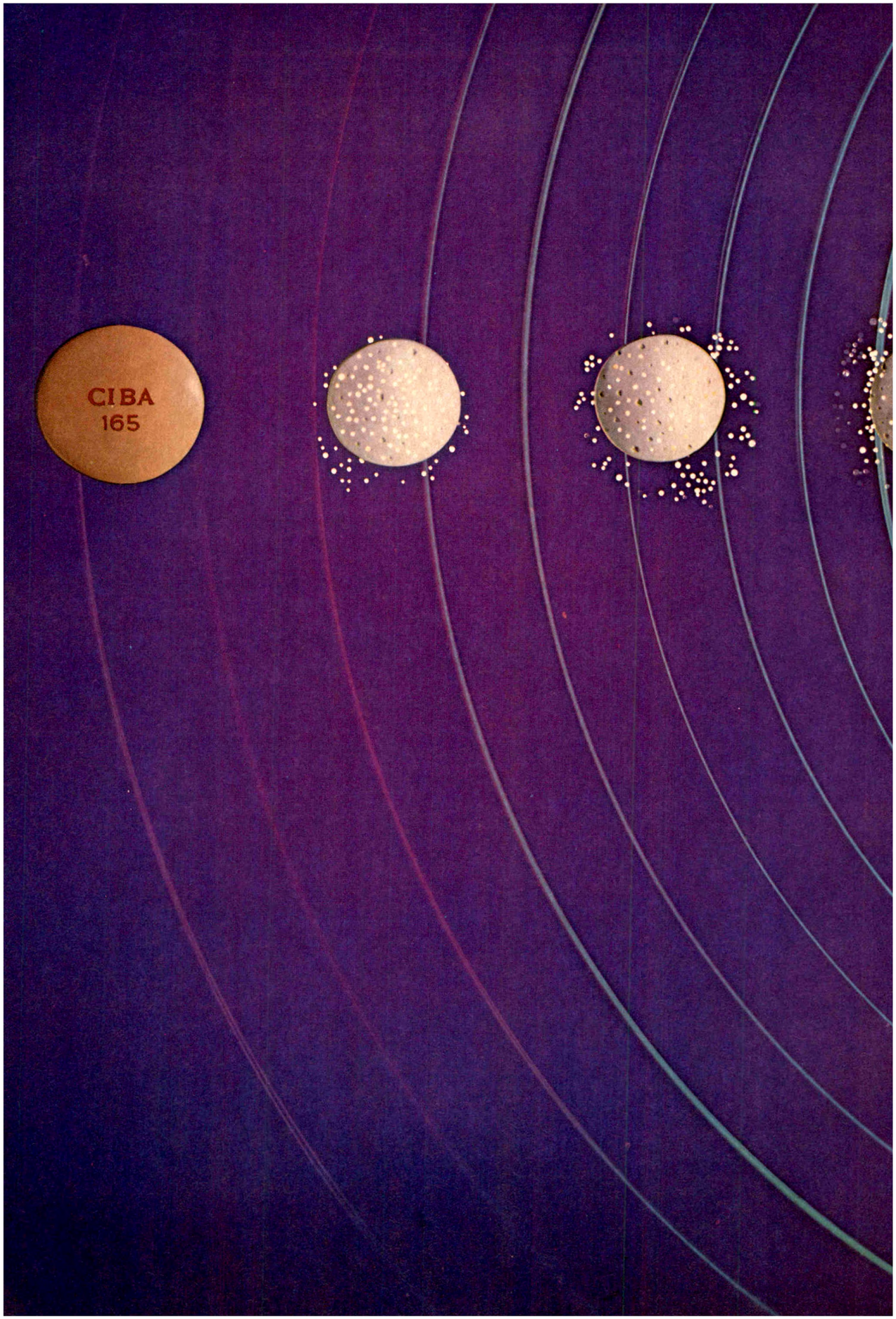
The prevalence, characteristics and clinical features of ventricular electrical instability assessed by programmed ventricular stimulation were studied in 50 hemodynamically stable patients 17 to 40 days after myocardial infarction. Ventricular electrical instability was defined as induction of 10 or more consecutive intraventricular reentrant beats. Of 50 patients, 23 (46%) had ventricular electrical instability (in 10 of whom sustained ventricular tachycardia was induced). During a mean follow up of 11.2 months no sudden death occurred. It is concluded that there is a high prevalence of ventricular electrical instability after acute myocardial infarction, not predicted by noninvasive tests.

395 Bretylium: Relations Between Plasma Concentrations and Pharmacologic Actions in High-Frequency Ventricular Arrhythmias

HENRY J. DUFF, DAN M. RODEN, AVRAHAM YACOBI, DAVID ROBERTSON, THEODORE WANG, REBECCA J. MAFFUCCI, JOHN A. OATES, and RAYMOND L. WOOSLEY

The relation between concentration and pharmacologic response to bretylium was assessed in 6 patients with high-frequency ventricular arrhythmia. Patients received bretylium at 2.5 mg/kg, 5 mg/kg, 10 mg/kg and placebo in a randomized sequence. Adrenergic neuronal blockade developed early and at a time when relatively small amounts of bretylium had been administered. The frequency of an early sympathomimetic response increased

Continued on page A41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Before prescribing, please consult brief Prescribing Information on next page.

CIBA

1. Data on file. CIBA Pharmaceutical Company.

SLOW-K® potassium chloride slow-release tablets

Brief Summary of Prescribing Information

DESCRIPTION

Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalemia: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years), cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS

The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

ADVERSE REACTIONS

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications, Warnings and Overdosage). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION

The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C82-58 (Rev 1-83)

Consult complete product literature before prescribing.

CLASSIFIED

The Department of Radiology of Harvard Medical School cooperation with the Council on Cardiovascular Radiology the American Heart Association will sponsor its annual cor nary angiography course, "Coronary Angiography 1985: Ne Developments in Diagnostic Techniques, PTCA and Thromb lytic Therapy", June 10-13, 1985 at the Hyatt Regency, Ca bridge, Mass. The program will consist of formal lectures in t mornings, and small group workshops in the afternoons. Wo shops will focus on cine techniques, intracoronary streptok ase, interpretation of coronary angiograms, digital cardi imaging, PTCA, as well as other topics. David C. Levin, M.D. Program Director. Harvard Medical School faculty include D Abrams, Adams, Block, Boxt, Cohn, Collins, Fallon, Ganz, Ha rington, Levin, Markis, Meyerovitz, Mudge, Paulin, Sasaha Selwyn, Taus, and Ms. Damiano. Guest faculty include D Faxon, Gould, Kent, Rentrop, Scheibe and Williams, a Messrs. Culverwell and Stueve. The fee is $425 for physicia $290 for residents, fellows and RTs. The course is approv for 29 Category 1 credits. For further information contact: Anne Latino, Coordinator of Continuing Education, Brigha and Women's Hospital, Department of Radiology, 75 Fran Street, Boston, MA 02115.

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with dosage and its occurrence was temporally related to the onset of adrenergic neuronal blockade, and increase in plasma norepinephrine. Increase in ventricular arrhythmia frequency occurred in relation to the sympathomimetic phase.

402 Continuous Electrical Activity During Sustained Monomorphic Ventricular Tachycardia: Observations on Its Dynamic Behavior During the Arrhythmia

PEDRO BRUGADA, HOSHIAR ABDOLLAH, and HEIN J.J. WELLENS

Catheter mapping during monomorphic ventricular tachycardia (VT) revealed continuous electrical activity in 20 of 56 consecutive patients (in 15 of 42 with old myocardial infarction, 5 of 6 with right ventricular dysplasia and 0 of 8 with idiopathic VT). In 17 of 20 patients showing continuous electrical activity during VT at least 1 of the following observations was made: (1) Spontaneous disappearance of continuous electrical activity without changes in rate, morphology or axis of VT. (2) Pacing-induced transient termination of continuous electrical activity without termination of VT. (3) Spontaneous disappearance of continuous electrical activity during VT as a rate-dependent phenomenon. (4) Wenckebach-like conduction to other areas resulting in transient and periodic continuous electrical activity. (5) Dependence of continuous electrical activity from ventricular activation pattern during VT. (6) Pacing-induced change from noncontinuous electrogram into continuous electrical activity without prevention of termination of VT. (7) Termination of continuous electrical activity following antiarrhythmic drugs without termination of VT. These observations demonstrate that several electrophysiologic phenomena can simulate continuous electrical activity during monomorphic VT. Transient continuous electrical activity is a frequent phenomenon representing electrical activity from abnormal areas not necessarily required to perpetuate VT.

412 Arrhythmias Induced During Termination of Supraventricular Tachycardia

BERND WALDECKER, PEDRO BRUGADA, KAREL den DULK, MANFRED ZEHENDER, and HEIN J.J. WELLENS

To evaluate arrhythmias induced by attempted termination of supraventricular tachycardia (SVT), 453 attempts to interrupt SVT by pacing in 111 patients were analyzed. Seventy-six patients had SVT using an accessory atrioventricular bypass and 35 patients had intranodal SVT. The extrastimulus technique and overdrive pacing were performed from the atrium and ventricle. Atrial flutter or fibrillation, other SVT, nonsustained ventricular tachycardia, as well as inability to terminate SVT without initiating another arrhythmia, were observed. Pacing-induced arrhythmias during attempted termination of SVT were evaluated qualitatively and quantitatively. Assessment of the safety of antitachycardia pacing by careful investigation during programmed electrical stimulation is mandatory in every patient before considering use of an antitachycardia pacemaker for treatment of SVT.

SYSTEMIC HYPERTENSION

418 Maximal Hand Blood Flow in Hypertensive and Normal Subjects

DAVID HORWITZ and DALI J. PATEL

Hypertensive and normal subjects were studied under conditions of maximal vasodilation wherein flow at a given driving pressure was considered to give an index of structural changes in resistance vessels. Flow was measured by venous occlusion plethysmography after 10 minutes of ischemia, and arterial pressure was measured by the arm cuff method. Flow at a transmural pressure of 85 mm Hg was calculated for each subject. Mean flow for normal subjects was 41 ml/100 ml/min and differed significantly from that of the patients with sustained hypertension (30 ml/100 ml/min).

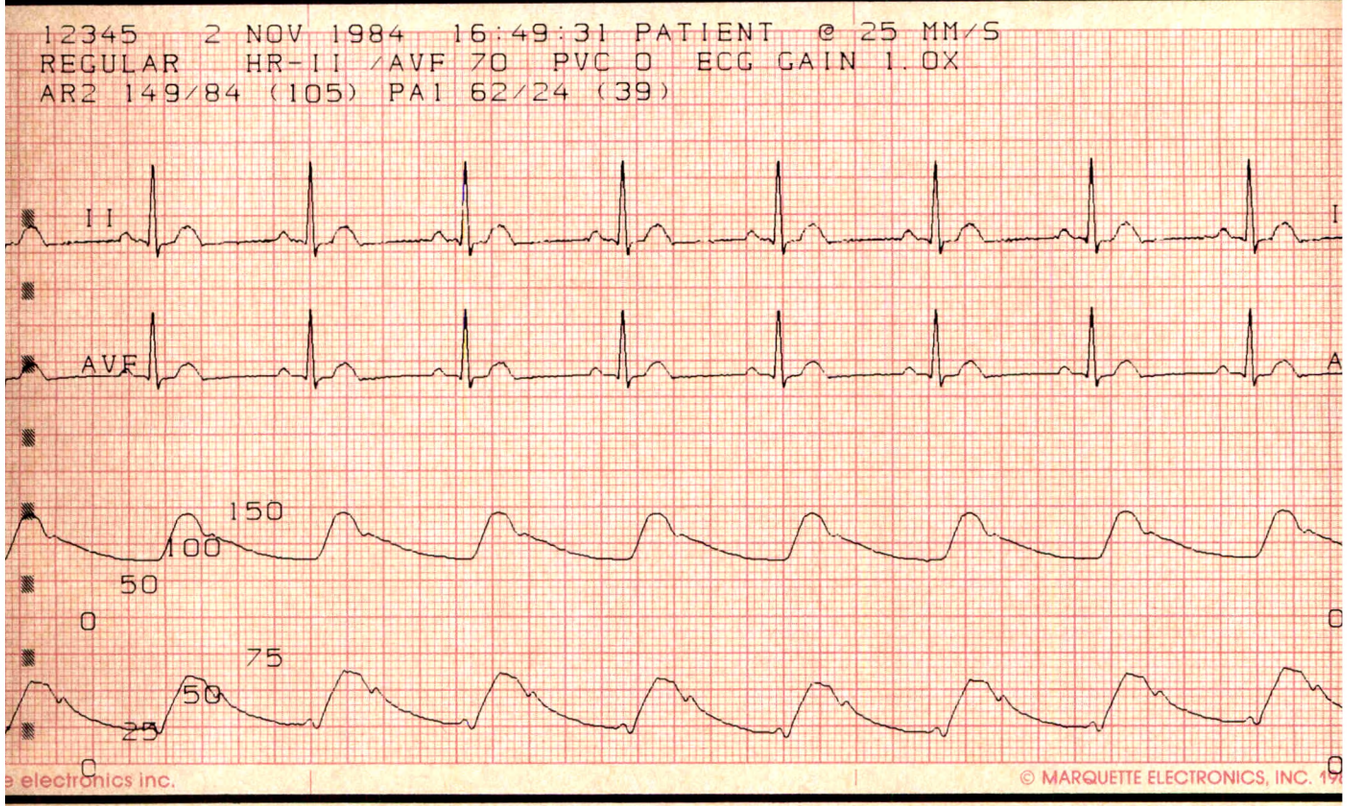
CONGESTIVE HEART FAILURE

423 Vascular Hemodynamic Impedance in Congestive Heart Failure

STANLEY M. FINKELSTEIN, JAY N. COHN, V. ROSS COLLINS, PETER F. CARLYLE, and WENDA J. SHELLEY

Differences in peripheral vascular state between patients with congestive heart failure (CHF) and the healthy population were determined by pulse-contour analysis. Vascular hemodynamic impedance parameters (compliance and resistance) were determined from brachial artery pressure waveforms recorded from a group of 14 patients and 7 healthy control subjects using computer analysis of the diastolic waveforms and a modified Windkessel model of the circulation. Cardiac output, heart sounds and electrocardiograms were also monitored. Mean arterial pressure was similar in the 2 groups, but cardiac output was significantly lower and heart rate significantly higher in the CHF group than in the healthy control subjects. Systemic vascular resistance was slightly

Documentation



2 ECG traces; 2 pressure traces; real time data

Marquette Electronics' Direct Digital Writer redefines patient monitoring documentation

A considerable amount of vital information can be displayed on your monitor screen . . . trends, ECG histories, stored data, simultaneous waveforms from many parameters . . . but, until now, getting fast, accurate documentation of that information has been impossible.

The Direct Digital Writer (DDW) from Marquette Electronics has rewritten the rules that used to limit documentation. Now, any information you can display on your monitor screen can be printed in hardcopy using just one device, not two as with most other systems. With the DDW, you can simultaneously plot four physiological waveforms in real time, quickly and accurately print stored data, and print any combination of stored and real time data you need.

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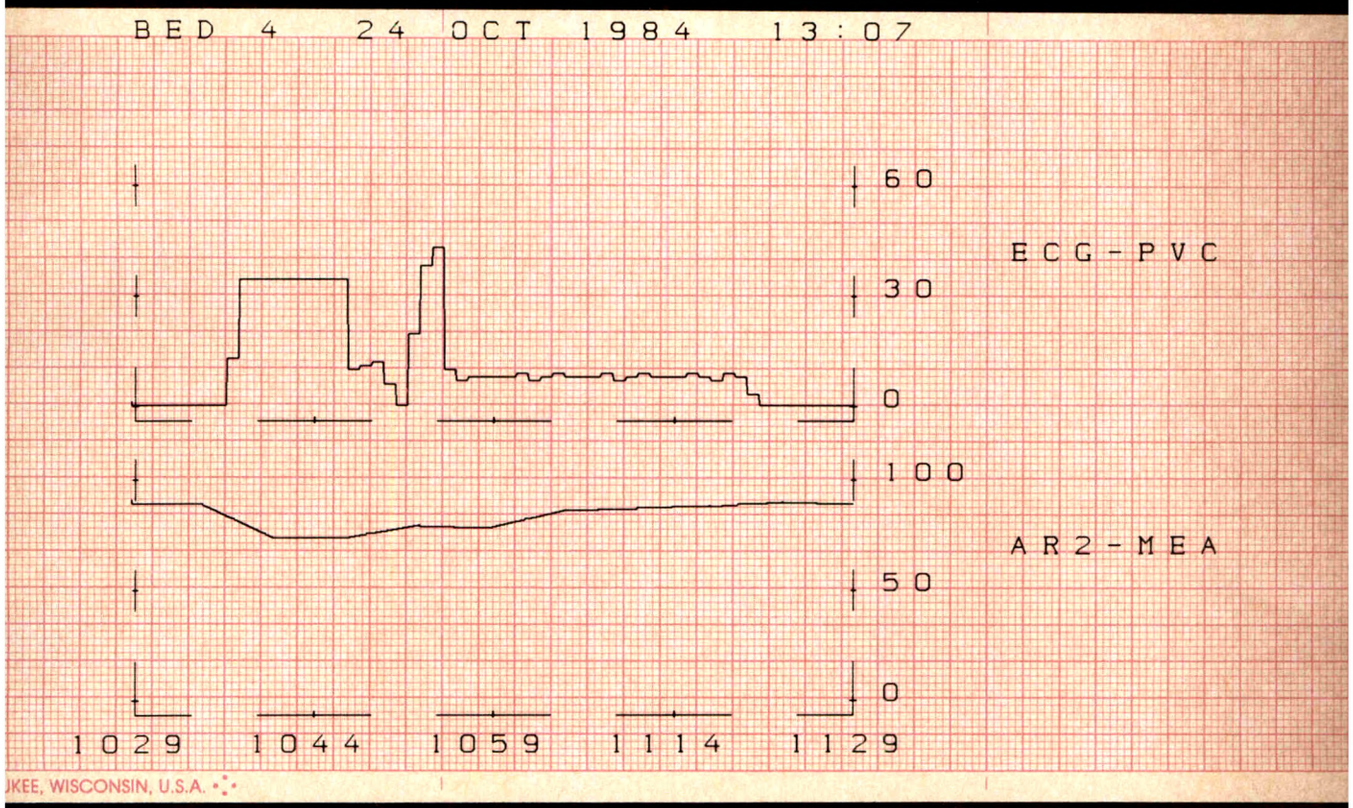

PVC and mean arterial pressure; trend of stored data

you have a precise reference at all times. And because the DDW has only one moving part—the paper drive—it's more accurate and reliable. Resolution and linearity far exceed those of conventional units because patient information is inscribed directly from digital waveforms (at an ECG resolution of 12.5 microvolts)... there's no distortion, no response problems, no overshoot or damping problems.

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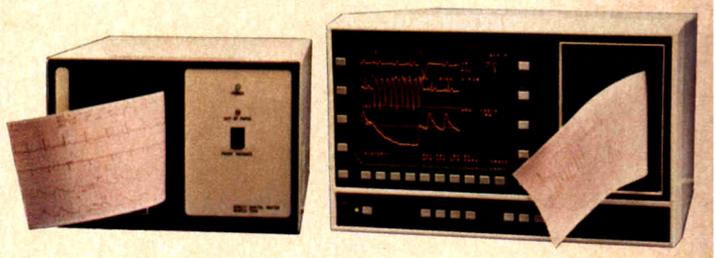

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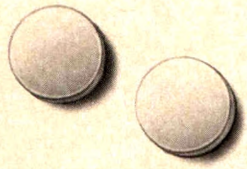
Generic methyldopa tablets* do contain sodium metabisulfite



Artist's interpretation of
generic methyldopa tablets*

"This product contains Sodium Metabisulfite as a preservative, which may cause allergic-type reactions in certain susceptible persons, especially asthmatics."

(from the Description and Precautions Sections of the Package Circular for generic methyldopa tablets*)

*as manufactured by Cord Laboratories, Inc.

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ALDOMET® (Methyldopa | MSD) tablets do not

TABLETS: 500 mg, 250 mg, and 125 mg

While the presence of sodium metabisulfite is probably important in a limited number of patients, it could be a factor in deciding whether to allow substitution for a prescription of ALDOMET®.

Although Tablets ALDOMET® do not contain any sulfite preservatives, as the Prescribing Information indicates, Oral Suspension ALDOMET® (Methyldopa, MSD) and Injection ALDOMET® Ester HCl (Methyldopate HCl, MSD) do contain sodium bisulfite as a preservative.

The use of any of these products is contraindicated in hypersensitive patients, in active hepatic disease, or if previous methyldopa therapy has been associated with liver disorders.

For a Brief Summary of Prescribing Information, please see following page.

MSD
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A45

ALDOMET® (METHYLDOPA|MSD)

ALDOMET® Ester HCl (METHYLDOPATE HCl|MSD)

Tablets, containing 125, 250, or 500 mg methyldopa. Oral Suspension, containing 250 mg methyldopa per 5 ml and alcohol 1% with benzoic acid 0.1% and sodium bisulfite 0.2% added as preservatives. Injection for intravenous use, containing per 5 ml: methyldopate hydrochloride 250.0 mg; inactive ingredients—citric acid anhydrous 25.0 mg, disodium edetate 2.5 mg, monothioglycerol 10.0 mg, sodium hydroxide to adjust pH, and methylparaben 7.5 mg, propylparaben 1.0 mg, and sodium bisulfite 16.0 mg added as preservatives.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions. With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood. At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients. Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. A paradoxical pressor response has been reported with intravenous use. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Nervous System/Psychiatric:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Paradoxical pressor response with intravenous use. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear) *Digestive:* Nausea, vomiting, distention, constipation, flatus, diarrhea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis, pericarditis. *Skin:* Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis. *Respiratory:* Nasal stuffiness. *Metabolic:* Rise in BUN. *Urogenital:* Breast enlargement, gynecomastia, lactation, amenorrhea, impotence, decreased libido. *Endocrine:* Hyperprolactinemia. *Musculoskeletal:* Mild arthralgia, with or without joint swelling; myalgia.

Note: Initial adult oral dosage should be limited to 500 mg daily in divided doses when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, PA 19486

J4AM48(717;026)

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CARDIOLOGIST: Ohio, BC/BE, with training in invasive and noninvasive procedures, M.D. degree must be from a U.S. medical school. Attractive salary. Please send curriculum vitae and references to: P.O. Box 290, The American Journal of Cardiology, 875 Third Ave., New York, N.Y. 10022.

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CARDIOLOGIST

BC/BE, non-invasive or invasive, to join large cardiology group. Midwest metropolitan setting. Send CV to Box 365, American Journal of Cardiology, 875 Third Avenue, New York, New York 10022.

higher in the CHF group, but there was considerable overlap between the 2 groups. Distal vascular compliance from pulse-contour analysis was significantly lower in the CHF group, and there was only minimal overlap between the groups. The data therefore suggest that distal compliance is a more sensitive and specific index than systemic vascular resistance to the vascular change in heart failure.

VALVULAR HEART DISEASE

428 Effects of Upright and Supine Position on Cardiac Resting and Exercise Response in Aortic Regurgitation

WEI FENG SHEN, GARY S. ROUBIN, PETER J. FLETCHER, CHRISTOPHER Y-P. CHOONG, BRIAN F. HUTTON, PHILLIP J. HARRIS, and DAVID T. KELLY

Upright and supine radionuclide ventriculography was performed in 15 patients with moderate to severe aortic regurgitation (AR) and 10 control subjects at rest and during exercise. In patients with AR, heart rate was higher during upright exercise, but blood pressure and left ventricular (LV) output were similar during both forms of exercise. LV stroke volume and end-diastolic volume were not altered during supine exercise. LV end-systolic volume and ejection fraction decreased during supine exercise, but both were unchanged during upright exercise. Of 15 patients, 5 in the upright position and 12 in the supine position had an abnormal LV ejection fraction response to exercise ($p < 0.01$). Right ventricular ejection fraction and regurgitant index were similar during both forms of exercise. Thus, LV response to exercise varies with posture in patients with moderate to severe AR.

431 Electrocardiographic Observations in Clinically Isolated, Pure, Chronic, Severe Aortic Regurgitation: Analysis of 30 Necropsy Patients Aged 19 to 65 Years

WILLIAM C. ROBERTS and PAUL J. DAY

Certain electrocardiographic findings are described in 30 necropsy patients with clinically isolated, pure, chronic, severe aortic regurgitation. Their ages ranged from 19 to 65 years (mean 45). The hearts of the 22 men weighed 430 to 1,100 g (mean 717) and of the 8 women 375 to 950 g (mean 638). Four had grossly visible left ventricular (LV) scars. The total 12-lead QRS amplitude in the 30 patients ranged from 109 to 428 mm (mean 272) (19 mm = 1 mV) and in 27 patients (90%) it was >175 mm. The mean QRS amplitude for each of the 12 leads averaged 23 mm. The highest mean QRS voltage occurred in leads V_2 and V_3 (each 38 mm), and the lowest in lead aVR (11 mm). The mean QRS voltage in lead V_5 was higher than that in V_6 (33 vs 28 mm) and in 22 patients (73%) the QRS voltage in V_5 was higher than in V_6. The sum of the S wave in V_1 plus the larger of the R wave in V_5 or V_6 (Sokolow-Lyon index) averaged 51 mm and in 22 patients (73%) it was >35 mm. The Romhilt-Estes voltage criteria for LV hypertrophy was fulfilled even less frequently.

439 Myxoid Degeneration of the Aortic Valve and Isolated Severe Aortic Regurgitation

WARREN M. ALLEN, JACK M. MATLOFF, and MICHAEL C. FISHBEIN

A clinicopathologic study to determine the cause of valve failure was undertaken on 55 patients undergoing valve replacement for pure AR. The clinical histories established a cause in 34 cases: rheumatic in 11, endocarditis in 13, congenital in 4, associated with aortic aneurysms in 4 and Marfan syndrome in 2. In the remaining 21 valves, 13 showed the pathologic finding of myxoid degeneration, defined as significant disruption of the valve fibrosa and its replacement by acid mucopolysaccharides and cystic change. The clinical features of the patients with myxoid degeneration of uncertain cause were as follows: male (85%), elderly (average age 63 years), with a long-standing history of hypertension (77%) and coronary artery disease (46%). Our findings indicate that myxoid degeneration of the aortic valve is a common pathologic endpoint (36% of all valves examined) and in a certain segment of patients may be associated with long-standing hypertension.

445 Value of Multiple Echocardiographic Views in the Evaluation of Aortic Stenosis in Adults by Continuous-Wave Doppler

GEORGE A. WILLIAMS, ARTHUR J. LABOVITZ, JEANNE G. NELSON, and HAROLD L. KENNEDY

Fifty-two patients referred for evaluation of aortic stenosis were examined with Doppler echocardiography to assess the effect of sampling the aortic valve gradient at different sites. Gradients from 0 to 136 mm Hg were adequately recorded from 51 of 52 patients. Maximal calculated gradients from each area were compared in all patients. Comparison of Doppler calculated peak gradient with cardiac catheterization was performed in 23 patients. Apical and right parasternal velocities were not significantly different and could be recorded in 90% of patients. Velocities from the suprasternal window were significantly lower and underestimation tended to in-

Continued on page A51

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Clinical Clues to MIXED ANGINA *No. 1*

Thirty seconds ago he was reading

He wasn't exercising; his myocardial oxygen demand didn't increase. Yet now he's having an angina attack.

That's the unpredictability of MIXED ANGINA—vasoconstriction coexisting with fixed coronary lesion, to produce a critical reduction of myocardial blood flow.

And because vasoconstriction is an unpredictable event, ischemia and pain occur unpredictably:

- at rest, or even during sleep
- at varying levels of exercise
- upon exposure to cold
- under emotional stress
- diurnally, typically in the morning

PROCARDIA® (nifedipine) is a primary therapy for the patient with MIXED ANGINA. It prevents vasoconstriction in both large coronary arteries and coronary arterioles to maintain myocardial blood flow and oxygen supply. At the same time, PROCARDIA dilates peripheral arteries to reduce afterload and myocardial oxygen demand.

As a result, PROCARDIA can significantly reduce your patient's angina attack rate and need for nitroglycerin!

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Primary Protection in
MIXED ANGINA

Please see PROCARDIA® (nifedipine) brief summary on next page.

Thirty seconds ago he was reading.

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PRIMARY PROTECTION IN MIXED ANGINA

Usual Effective Dosage: 30 to 60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level a a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and th patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration severity of angina on starting PROCARDIA or at the time of dosage increases.

A Favorable Safety Profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

Reference:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 106:644-652, 1983.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congesti heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricul dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline pho phatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA (nifedipine) therapy is uncerta in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical sym toms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have be reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregati and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has be demonstrated.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 p tients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocki agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination m increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controll studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal voluntee The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with cor nary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which goxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, a discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin a ticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80 and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently rece ing cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two yea and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a do approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, m and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used duri pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral eden nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5 palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cram nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cram flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balan dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, p pura, allergic hepatitis, gingival hyperplasia, and erythromelalgia. Very rarely, introduction of PROCARDIA therapy w associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocard infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular rhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CA SULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (N 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperat 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request. Revised January 1985 © 1982, Pfizer I

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LABORATORIES DIVISION
PFIZER INC.

crease with the age of the patient. Correlation of the maximal gradient from any window with cardiac catheterization was r = 0.861, and all patients with a gradient >50 mm Hg were accurately identified. Doppler echocardiography from multiple windows is a useful adjunct in the noninvasive evaluation of aortic stenosis.

450 Coronary Artery Luminal Diameter in Aortic Stenosis

SULTAN A. ABDULALI, B. GANESH BALIGA, ANDREW D. CLAYDEN, and DONALD R. SMITH

The coronary artery luminal diameter of 32 patients with aortic stenosis (AS) were compared by means of a derived index with 24 control subjects without left ventricular (LV) hypertrophy. Patients with AS had significantly larger coronary arteries than control subjects ($p < 0.01$). The increase in coronary luminal diameters had a weak correlation with LV wall thickness ($r = 0.32$) and LV mass ($r = 0.34$). In 21 patients with AS and normal coronary angiograms, there were no significant differences in coronary artery diameters, peak LV stress or LV tension at rest between patients with and those without angina.

454 Detailed Anatomy of the Normally Functioning Aortic Valve in Hearts of Normal and Increased Weight

MARC A. SILVER and WILLIAM C. ROBERTS

The area, weight and 4 linear measurements were made on each aortic valve cusp in 100 necropsy patients with normally functioning aortic valves, and the volume of each sinus of Valsalva and the aortic area at the sinotubular junction were determined in the same patients. The sums of the aortic valve cuspal areas, cuspal weights and sinus of Valsalva volumes increased with age ($p < 0.001$) and with heart weight ($p < 0.001$). All 3 variables (cuspal area, cuspal weight and sinus of Valsalva volume) also increased with age and heart weight relative to each other. The luminal area of aorta at the sinotubular junction also increased with age and heart weight, and it also increased as the sum of the aortic valve cuspal areas and weights and sinus of Valsalva volumes increased. In only 16% of the 100 patients were the 3 aortic valve cusps of similar size (<5% difference in area between cusps); in 51%, 1 cusp was of different size than the other 2, and in 33% of the patients all 3 cusps were of different sizes.

462 Echophonocardiographic Estimates of Pulmonary Artery Wedge Pressure in Mitral Stenosis

PETER S. RAHKO, JAMES A. SHAVER, ROSEMARIE SALERNI, WILLIAM H. GAMBLE, and P. S. REDDY

The accuracy of echophonocardiographic intervals for predicting pulmonary artery wedge (PAW) pressure or left atrial (LA) pressure was reviewed in 77 patients with mitral stenosis. The A_2-E and Q-C intervals were correlated both individually and in combination with PAW and LA pressures. The A_2-E interval correlation with mean PAW pressure was only modest, but improved when combined as a ratio or difference with the Q-C interval or when it was correlated with the V wave of PAW pressure. Atrial fibrillation decreased the predictive accuracy of all intervals. The best correlations were obtained when LA pressure was used, suggesting that damping of the PAW pressure also affects this relation. Thus, multiple factors affect the noninvasive estimates of PAW or LA pressures, but these predictive indexes may give valuable information when used appropriately.

CARDIOMYOPATHY

471 A Randomized Trial of Low-Dose Beta-Blockade Therapy for Idiopathic Dilated Cardiomyopathy

JEFFREY L. ANDERSON, JOAN R. LUTZ, EDWARD M. GILBERT, SHERMAN G. SORENSEN, FRANK G. YANOWITZ, RONALD L. MENLOVE, and MARIAN BARTHOLOMEW

Beta blockade to improve survival in idiopathic dilated cardiomyopathy (IDC) has been controversial, and randomized studies have not been performed. Thus, 50 patients with IDC were randomized and paired to standard therapy (C) alone or with β blockade (BB). Entry characteristics of the 2 groups were similar. Beta blockade with metoprolol was titrated from 12.5 to 50 mg twice daily as tolerated (final average dose 61 mg daily). Clinical follow-up averaged 19 months (range 1 to 38). Low-dose BB was tolerated in 80% of IDC patients on a long-term basis. By intention to treat, 5 BB and 6 C patients died (difference not significant). By actual treatment, 3 BB and 8 C patients died ($p = 0.12$). Functional class and exercise capacity favored those who received BB. IDC patients who received low-dose BB have a good prognosis. However, mortality in C patients is less than in retrospective studies. A larger, randomized multicenter study will be required for definitive evaluation of survival effects of BB in patients with IDC.

Continued on page A53

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MISCELLANEOUS TOPICS

476 Two-Dimensional Echocardiographically Guided Pericardiocentesis: Experience in 117 Consecutive Patients

JOHN A. CALLAHAN, JAMES B. SEWARD, RICK A. NISHIMURA, FLETCHER A. MILLER, Jr., GUY S. REEDER, CLARENCE SHUB, MARK J. CALLAHAN, THOMAS T. SCHATTENBERG, and A. JAMIL TAJIK

Pericardiocentesis guided by 2-dimensional echocardiography provides a safe and efficient way to remove pericardial fluid. It can be carried out as an emergency procedure and is versatile enough to satisfy routine diagnostic needs.

480 Magnetic Resonance Imaging of Constrictive Pericardial Disease

RENATE L. SOULEN, DAVID D. STARK, and CHARLES B. HIGGINS

Gated magnetic resonance imaging of 5 patients with suspected constrictive pericardial disease was performed using a superconducting magnet and compared with other noninvasive studies and with hemodynamic data. Hemodynamic data at catheterization in all patients was consistent with pericardial constriction. Pericardial thickness measured >5 mm in 4 patients and 5 mm in 1 patient with constrictive pericardial disease. Calcific deposits produced no magnetic resonance signal, whereas pericardial inflammation caused increased signal intensity of the thickened pericardium. Dilatation of the right atrium, vena cavae and hepatic veins and right ventricular narrowing was present in all patients. Magnetic resonance allows measurement of pericardial thickness *and* depicts internal cardiac anatomy without using radiation or contrast medium. This early experience suggests it is the imaging method of choice in the diagnosis of constrictive pericardial disease.

485 The King of Hearts: Analysis of 23 Patients with Hearts Weighing 1,000 Grams or More

WILLIAM C. ROBERTS and MICHAEL J. PODOLAK

Certain clinical and morphologic features are described in 23 patients in whom the heart at necropsy weighed ≥1,000 g (mean 1,106). The heart weight to body weight ratio ranged from 1.2 to 2.7 (normal 0.40). The 23 patients were derived from examination of the hearts of 7,671 patients with various cardiovascular disorders in a 25-year period. The massive cardiomegaly was the result of aortic regurgitation (AR) in 14 patients (61%): isolated in 8, associated with mitral regurgitation in 4, and associated with ventricular septal defect in 2. Three others (13%) had combined aortic valve stenosis and aortic regurgitation and 1 patient (4%) had mitral stenosis and regurgitation and mild aortic stenosis. Four patients (17%) had hypertrophic cardiomyopathy, and 1 patient (4%) had ventricular septal defect with mitral stenosis. They were 20 to 64 years old (mean 42) and 21 (91%) were men. Four patients at necropsy had 1 or more major coronary arteries narrowed >75% in cross-sectional area by atherosclerotic plaques, and only 4 patients had grossly visible left ventricular (LV) scars, 2 of whom had insignificant coronary narrowing. Examination of electrocardiograms in 17 of the 23 patients disclosed that Sokolow-Lyon criteria for LV hypertrophy was achieved in only 12 patients (71%) and Romhilt-Holt QRS voltage criteria faired even worse. Total 12-lead QRS voltage was >175 mm (10 mm = 1 mV) in 16 patients (94%) and >250 mm in 13 patients (76%). The total 12-lead QRS voltage in 17 patients ranged from 140 to 601 mm (mean 323). Measurement of the sum of 12-lead QRS voltage may be quite useful in diagnosing LV hypertrophy by electrocardiogram.

495 Detection of Platelet Deposition at the Site of Peripheral Balloon Angioplasty Using Indium-111 Platelet Scintigraphy

CHRISTOPHER F. POPE, MICHAEL D. EZEKOWITZ, EILEEN O. SMITH, STANLEY RAPOPORT, MORTON GLICKMAN, H. DIRK SOSTMAN, and BARRY L. ZARET

To determine whether platelet deposition at the site of balloon angioplasty could be detected using indium-111 platelet scintigraphy, 15 patients aged 60 ± 9 years (mean ± standard deviation) undergoing iliac or femoral (n = 12), renal (n = 2) and distal aortic (n = 1) dilatations were studied. All patients received intravenous heparin at time of dilatation. In 11 of 12 patients with iliac and/or femoral dilatations, focal uptake was observed. In 4 patients (2 with renal artery stenoses, 1 iliofemoral and 1 distal aortic) uptake at the dilatation site was not detect-

Continued on page A57

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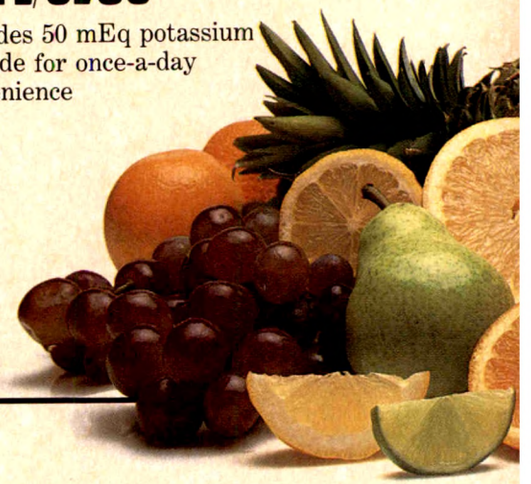

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K-Lyte/Cl® Each tablet in solution provides the equivalent of 25 mEq (1865 mg) potassium chloride (supplied by 1.5 gm potassium chloride, 0.5 gm potassium bicarbonate and 0.91 gm L-lysine monohydrochloride) and 0.55 gm citric acid.

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K-Lyte/Cl 50 and K-Lyte/Cl are oral potassium and chloride supplements. Each K-Lyte/Cl® 50 mEq tablet in solution provides the equivalent of 50 mEq (3730 mg) potassium chloride (supplied by 2.24 gm potassium chloride, 2.0 gm potassium bicarbonate and 3.65 gmL-lysine monohydrochloride) and 1.0 gm citric acid.

Each K-Lyte/Cl® tablet in solution provides the equivalent of 25 mEq (1865 mg) potassium chloride (supplied by 1.5 gm potassium chloride, 0.5 gm potassium bicarbonate and 0.91 gm L-lysine monohydrochloride) and 0.55 gm citric acid.

INDICATIONS AND USAGE

All K-Lyte® products are used for therapy or prophylaxis of potassium deficiency. They are useful when thiazide diuretics, corticosteroids, or vomiting and diarrhea cause excessive potassium loss; and when dietary potassium is low. These products may also be useful when potassium therapy is indicated in digitalis intoxication. K-LYTE/Cl and K-LYTE/Cl 50 are recommended in the management of hypokalemia accompanied by metabolic alkalosis and hypochloremia, e.g., as induced by vomiting.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions; chronic renal impairment, metabolic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns or adrenal insufficiency. Hypokalemia should not be treated by the concomitant administration of potassium salts and potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

WARNINGS

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and may be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

PRECAUTIONS

General precautions — The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. When interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of reduced total body potassium. Therefore, the treatment of potassium depleti requires careful attention to acid-base balance and appropriate monitoring of serum electroly the ECG, and the clinical status of the patient.

Information for Patients

To minimize the possibility of gastrointestinal irritation associated with the oral ingestio concentrated potassium salt preparations, patients should be carefully directed to dissolv dose completely in the stated amount of water.

Laboratory Tests

Frequent clinical evaluation of the patient should include ECG and serum potassium determinations.

Drug Interactions

The simultaneous administration of potassium supplements and a potassium-sparing diuretic produce severe hyperkalemia (see Contraindications).

Potassium supplements should be used cautiously in patients who are using salt substitu because most of the latter contain substantial amounts of potassium. Such concomitant use co result in hyperkalemia.

Usage in Pregnancy

Pregnancy Category C — Animal reproduction studies have not been conducted with any of t K-LYTE products. It is also not known whether these products can cause fetal harm wh administered to a pregnant woman or can affect reproduction capacity. They should be given a pregnant woman only if clearly needed.

Nursing Mothers

Many drugs are excreted in human milk and because of the potential for serious adverse react in nursing infants from oral potassium supplements, a decision should be made whether discontinue nursing or discontinue the drug, taking into account the importance of the d the mother.

Usage in Children

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The most common adverse reactions to oral potassium supplements are nausea, vomiting, dia and abdominal discomfort. These side effects occur more frequently when the medicatio taken with food or is not diluted properly or dissolved completely.

Hyperkalemia occurs only rarely in patients with normal renal function receiving potassi supplements orally. Signs and symptoms of hyperkalemia are cardiac arrhythmias, ment confusion, unexplained anxiety, numbness or tingling in hands, feet or lips, shortness of or difficult breathing, unusual tiredness or weakness and weakness or heaviness of legs Contraindications, Warnings and Overdosage).

How Supplied

K-Lyte/Cl® Effervescent Tablets (citrus or fruit punch flavors) are available in cartons of 30, and 250. K-Lyte/Cl® 50 Effervescent Tablets (citrus or fruit punch flavors) are available in ca of 30 and 100. Each tablet is individually foil wrapped.

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ed. Thus, despite the use of intravenous heparin, platelet accumulation at the site of peripheral angioplasty was detected using indium-111 platelet scintigraphy in most patients. These preliminary data illustrate the potential value of indium-111 platelet scintigraphy in the assessment of local platelet deposition in the restenosis process.

EDITORIALS

499 "Submaximal" Predischarge Exercise Testing After Acute Myocardial Infarction: Who Needs It?
ROBERT F. DeBUSK and CHARLES A. DENNIS

501 Billowing, Floppy, Prolapsed or Flail Mitral Valves?
JOHN B. BARLOW and WENDY A. POCOCK

503 FROM THE EDITOR

CME test on page 470

INSTRUCTIONS TO AUTHORS on page 498

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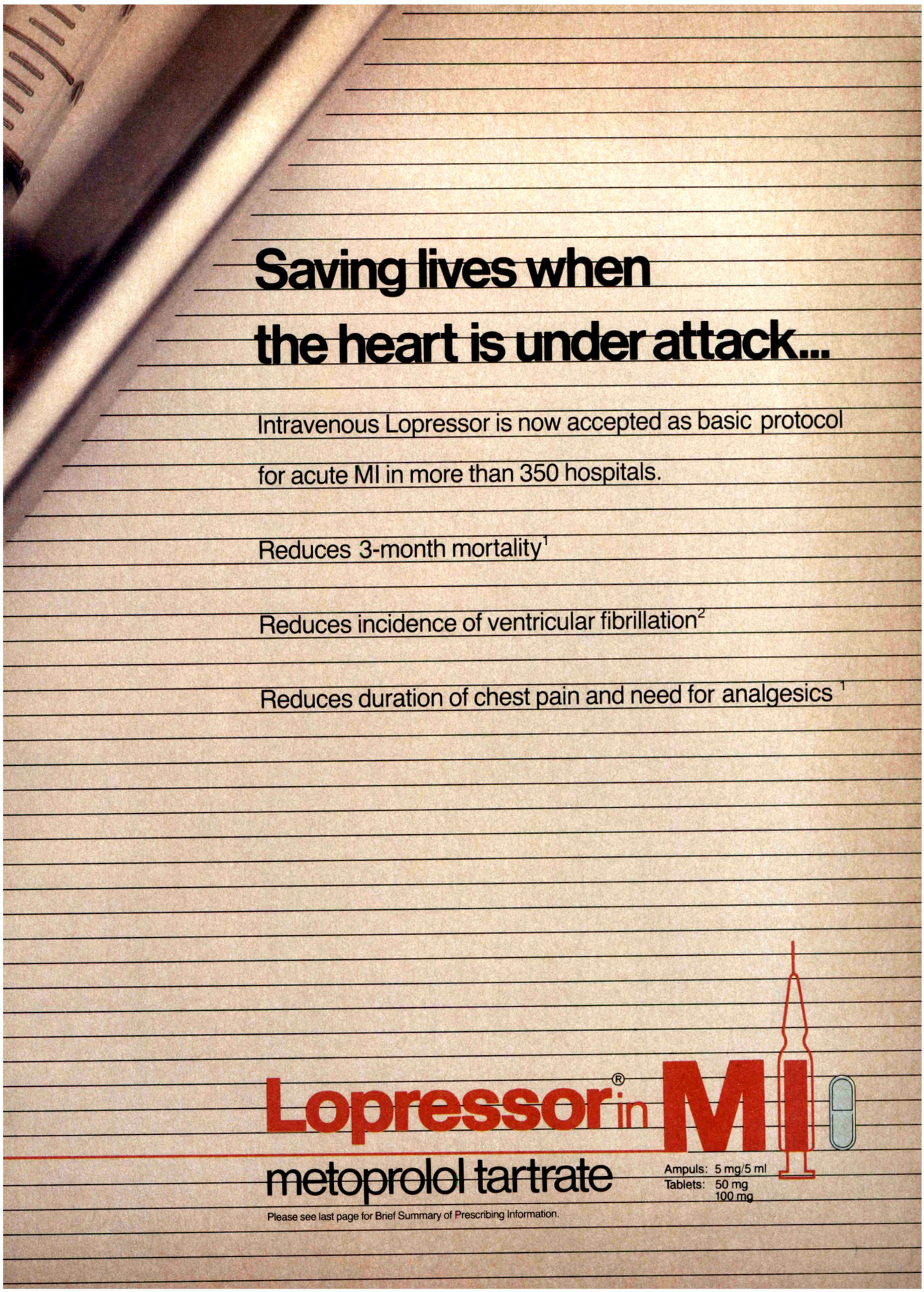
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Reduces incidence of ventricular fibrillation[2]
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The combination of early intravenous administration of Lopressor followed by long-term oral therapy resulted in a 36% reduction of three-month mortality in patients with definite or suspected acute MI in the Göteborg Trial.[1]

Treatment should be continued for 1-3 years.

Lopressor is contraindicated in patients with a heart rate <45 beats/min; significant heart block greater than first degree (P-R interval ≥0.24 sec); systolic blood pressure <100 mmHg; or moderate-to-severe cardiac failure. Please see last page for Brief Summary of Prescribing Information.

1. Hjalmarson Å, et al: The Göteborg Metoprolol Trial: Effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983 (June); 67(suppl 1):I-26-I-32.
2. Rydén L, et al: A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias. *N Engl J Med* 1983 (Mar 17); 614-617.

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(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Myocardial Infarction
Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first-(P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent $beta_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a $beta_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and $beta_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness. Patients should contact the physician if any difficulty in breathing occurs, and before surgery of any type, the patient should inform the physician or dentist that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a 1-year study in dogs, there was no evidence of drug-induced toxicity at or below oral dosages of 105 mg/kg per day. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.
Pregnancy Category B
Reproduction studies have been performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg and have revealed no evidence of impaired fertility or teratogenicity due to Lopressor. Increased postimplantation loss and decreased neonatal survival did occur in the rats (threshold between 50 and 500 mg/kg), and distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

DOSAGE AND ADMINISTRATION
Myocardial Infarction
Early Treatment: During the early phase of definite or suspected acute myocardial infarction, treatment with Lopressor can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of Lopressor each; the injections should be given at approximately 2-minute intervals. During the intravenous administration of Lopressor, blood pressure, heart rate, and electrocardiogram should be carefully monitored.

In patients who tolerate the full intravenous dose (15 mg), Lopressor tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (see ***Late Treatment*** below).

Patients who appear not to tolerate the full intravenous dose should be started on either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with Lopressor should be discontinued (see **WARNINGS**).

Late Treatment: Patients with contraindications to treatment during the early phase of suspected or definite myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on Lopressor tablets, 100 mg twice daily, as soon as their clinical condition allows. Therapy should be continued for at least 3 months. Although the efficacy of Lopressor beyond 3 months has not been conclusively established, data from studies with other beta blockers suggest that treatment should be continued for 1-3 years.

Note: **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

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Tablets: 50 mg 100 mg

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FEBRUARY 1, 1985

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NUMBER 4

CORONARY HEART DISEASE

Medically Directed At-Home Rehabilitation Soon After Clinically Uncomplicated Acute Myocardial Infarction: A New Model for Patient Care

ROBERT F. DeBUSK, MD, WILLIAM L. HASKELL, PhD, NANCY H. MILLER, RN, KATHY BERRA, RN,* and CRAIG BARR TAYLOR, MD, *In Cooperation with* WALTER E. BERGER III, MD, *and* HENRY LEW, MD

Medically directed at-home rehabilitation was compared with group rehabilitation which began 3 weeks after clinically uncomplicated acute myocardial infarction (AMI) in 127 men, mean age 53 ± 7 years. Between 3 and 26 weeks after AMI, adherence to individually prescribed exercise was equally high (at least 71%), the increase in functional capacity equally large (1.8 ± 1.0 METs) and nonfatal reinfarction and dropout rates equally low (both 3% or less) in the 66 men randomized to home training and the 61 men randomized to group training. No training-related complications occurred in either group. The low rate of reinfarction and death (5% and 1%, respectively) in the study as a whole, which included 34 patients with no training and 37 control patients, reflected a stepwise process of clinical evaluation, exercise testing at 3 weeks and frequent telephone surveillance of patients who underwent exercise training. Medically directed at-home rehabilitation has the potential to increase the availability and to decrease the cost of rehabilitating low-risk survivors of AMI.

(Am J Cardiol 1985;55:251–257)

Early evaluation of prognosis after acute myocardial infarction (AMI) has in recent years emerged as an important focus of standard medical care for this condition. Exercise testing performed alone or in conjunction with radionuclide imaging techniques effectively distinguishes high-risk and low-risk patients 10 to 21 days after AMI.[1–6] The use of early exercise testing to identify very low risk patient subsets (i.e., mortality rate less than 2% after AMI[1–3]), enables earlier rehabilitation of these patients. In a previous study from this laboratory, the functional capacity of patients who underwent medically supervised group exercise training 3 to 11 weeks after clinically uncomplicated AMI exceeded that of control subjects with no training.[7] The present study was designed to determine whether exercise training performed at home 3 to 26 weeks after clinically uncomplicated AMI was as safe and effective as medically supervised group training.

From the Division of Cardiology, Department of Medicine, Stanford University School of Medicine, Stanford, California; the Department of Medicine, Permanente Medical Group Incorporated, Redwood City; and Department of Medicine, Permanente Medical Group, Santa Clara, California. This study was supported by Grant HL18907 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland and by a grant from the PepsiCo Foundation, Purchase, New York. Manuscript received August 29, 1984; revised manuscript received October 24, 1984, accepted October 25, 1984.

* With the collaboration of YMCArdiac Therapy Programs in Palo Alto and San Jose, California.

Address for reprints: Robert F. DeBusk, MD, Stanford Cardiac Rehabilitation Program, 730 Welch Road, Palo Alto, California 94304.

Methods

Patients: Patients were admitted to Kaiser Permanente hospitals in Redwood City and Santa Clara, California between July 1, 1979 and July 1, 1983. AMI was documented by the combination of characteristic elevation of serum creatine kinase or oxaloacetic transaminase, a history of prolonged chest pain consistent with AMI and the appearance of new Q waves or evolutionary ST changes. Of the 378 consecutive men aged 70 years or younger considered for the study, 175 were excluded because of conditions that precluded symptom-limited treadmill testing 3 weeks after AMI: cardiac exclusions in 112 patients for congestive heart failure, unstable angina pectoris, valvular heart disease, atrial fibrillation, bundle branch block, and a history of coronary artery bypass surgery; noncardiac exclusions in 38 patients for stroke, limiting orthopedic abnormalities, peripheral vascular disease, chronic obstructive pulmonary disease and obesity, and patient or physician refusal in 10 and 15 patients, respectively.

The remaining 203 patients considered eligible to undergo symptom-limited treadmill testing 3 weeks after AMI were randomized to 1 of 6 groups that represented 4 basic assignments (Fig. 1): exercise testing followed by exercise training at home for a duration of 23 weeks (extended training—group 1A) or 8 weeks (brief training—group 1B), or in a gymnasium for 23 weeks (extended training—group 2A) or 8 weeks (brief training—group 2B), exercise testing without subsequent exercise training (group 3) and control (neither exercise testing nor training—group 4).

Five patients were excluded after randomization because of moderately severe angina or signs of congestive heart failure during treadmill exercise testing. Of these, 3 underwent coronary artery bypass surgery, 1 experienced nonfatal reinfarction and 1 had no subsequent cardiac event.

The 161 patients who remained in the trial after 3 weeks of exercise testing and the 37 control patients constitute the training study. Exercise testing was scheduled for all but control patients 11 weeks after AMI and for all patients 26 weeks after AMI.

The mean age of the 198 training study participants was 52 ± 9 years. Infarction was inferior in 54%, anterior in 31% and transmural in 15% of patients. A history of old infarction or angina pectoris 3 months or more before AMI was noted in 7 and 24% of patients, respectively. Before AMI, 14% of the patients were retired. The remaining 86% were employed in the following categories: professional/mangerial, 56%; clerical/sales, 15%; and manual labor, 15%. Medical and demographic characteristics were not significantly different among the groups.

Among patients who underwent exercise testing at 3 weeks, the proportion receiving β-blocking drugs, long-acting nitrates and antiarrhythmic medications (procainamide, quinidine and disopyramide) was 11, 17 and 6%, respectively, without significant intergroup differences. The proportion of patients who received these medications at 26 weeks was 24, 22 and 11%, respectively, without significant intergroup differences. On both occasions these drugs were discontinued 48 to 72 hours before testing.

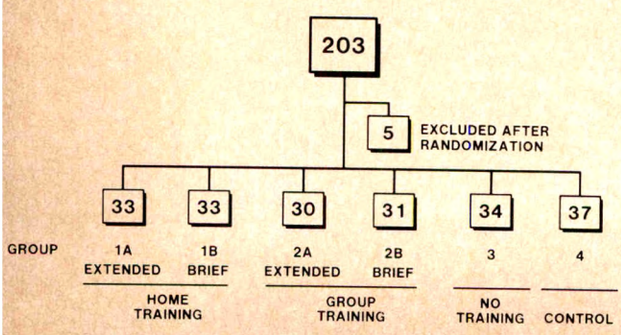

FIGURE 1. Random assignment of subjects.

Exercise testing: Symptom-limited treadmill testing was performed using protocols described by Naughton et al,[8] with 12-lead electrocardiographic monitoring and blood pressure recording by cuff sphygmomanometer. Exercise was terminated by: (1) limiting symptoms of chest pain, dyspnea, fatigue or leg cramps; (2) hypotension (a decrease in systolic pressure of at least 10 mm Hg from the peak value attained earlier during exercise); or (3) ventricular tachycardia (3 consecutive premature ventricular complexes). No complications in exercise testing occurred.

Patient counseling: After exercise testing at 3 weeks, patients and their spouses met with the program physician for 30 to 45 minutes to discuss the implications of the exercise test for further management. The patients were advised that test results would be provided to their private physicians who would retain responsibility for their medical management. The patients' capacity to resume customary preinfarctional physical activities with safety was discussed in detail. Patients and spouses then met with the program nurse for 30 to 45 minutes to discuss medication adherence and adverse effects, smoking, dietary habits and sexual activity. Patients assigned to home or group training were instructed by the nurse in carrying out their individualized exercise plan. "No-training" patients received no specific exercise prescription.

Exercise training prescription: The training heart-rate range for group and home training was 70 to 85% of the peak treadmill heart rate achieved at 3 and 11 weeks. Because peak exercise heart rate increases significantly by the seventh week after clinically uncomplicated AMI,[7] the training heart-rate range during weeks 8 to 11 was based on 100% of the peak 3-week treadmill heart rate or 85% of age-predicted peak heart rate, whichever was less. The average training range 3 to 7, 8 to 11 and 11 to 26 weeks was 96 to 117 , 105 to 121 and 110 to 129 beats/min, respectively. At 11 weeks, exercise cycles and heart rate monitors were withdrawn from patients assigned to brief home training, and paid participation in the YMCArdiac Therapy Program was terminated for patients who underwent brief group training.

Home training: Patients received detailed, written instructions involving all aspects of the home training program, including recognition of important changes in clinical status, such as worsening of angina pectoris and the appearance of unusual dyspnea or other conditions precluding exercise training. In the event of a change in clinical status, patients were advised to defer exercise training and to contact the program nurse or private physician.

Patients assigned to home training who were free of treadmill angina at 3 weeks (n = 55) were loaned stationary cycles (Tunturi), whereas those with treadmill angina at 3 weeks (n = 11) were instructed to walk briskly. All patients were instructed to exercise continuously for 30 minutes, 5 days/week. Exercise training sessions consisted of 5 minutes of warm-up, 20 minutes within the prescribed training heart-rate range and 5 minutes of cool-down.

Patients were loaned portable ExerSentry heart rate monitors (Respironics, Inc., Monroeville, Pennsylvania) to assist them in remaining within their prescribed heart-rate range during home training. These devices emit an audible tone whenever the heart rate is above or below the preset range and remain silent when the heart rate is within this range. A portable CardioBeeper monitor (Survival Technology, Inc.,

TABLE I Frequency of Treadmill-Induced Ischemic ST-Segment Depression or Angina Pectoris

	Groups					
	1A	1B	2A	2B	3	4
3 Weeks	14 of 33 (42%)	11 of 33 (33%)	4 of 30 (13%)	10 of 31 (32%)	9 of 34 (26%)	—
26 Weeks	9 of 26 (35%)	8 of 29 (28%)	3 of 26 (12%)	8 of 26 (31%)	8 of 25 (32%)	9 of 28 (32%)

Bethesda, Maryland) was used to transmit the electrocardiogram over the telephone to a strip-chart recorder located in the research unit. At prearranged times twice weekly, the program nurse telephoned patients at home to transmit an M-CL5 bipolar lead electrocardiogram during 1 minute of exercise within the training heart-rate range and during 1 minute of immediate recovery.

These telephone calls permitted verification of the training intensity and detection of changes in patients' clinical status and medication use. Adherence to training was also evaluated by the nurse's review of daily exercise training logs. These logs, which included duration and intensity of training as judged from heart rates displayed on ExerSentry monitors, were mailed to the program nurse every 2 weeks. No complications of home exercise training occurred.

Group training: Under the supervision of 2 nurses or 1 nurse and 1 physician, patients exercised with 20 to 35 other cardiac patients in the YMCArdiac Therapy programs in Palo Alto and San Jose, California. Three 1-hour training sessions per week were divided among 10 to 15 minutes of warm-up calisthenics, 30 to 40 minutes of walk/jog conditioning cycling and 10 to 15 minutes of cool-down walking and stretching, producing the same total duration of exercise within the training range as for home training (i.e., approximately 100 min/week). Guidelines for increasing the intensity of group training at 8 and 11 weeks were identical to those for home training. The program staff documented patients' participation in a manner similar to that for home training: training heart rate and exercise duration, medication use, clinical status and reasons for no attendance were tabulated. Electrocardiographic monitoring was not routinely performed; no complications of group exercise training occurred.

Documentation of nonprescribed exercise: Patients were interviewed at 11 and 26 weeks concerning the frequency and duration of walking and the intensity and duration of other aerobic-type leisure activities since hospitalization or their last clinic visit. To avoid influencing their physical activity habits, control patients were interviewed only at 26 weeks.

Data were collected separately for nonprescribed walking (i.e., equivalent to a workload of less than 4 METs, which would not be expected to lead to a training effect) and for more vigorous nonprescribed exercise (i.e., 4 METs or more, which would be expected to lead to such an effect).[9] The intensity of the latter was approximated from the known energy cost of various activities.[10] The total amount of exercise performed was calculated as MET minutes per day. For example, a patient who performed 10 minutes of a 5-MET activity was judged to have completed a total of 50 MET minutes of activity. The same method was used to quantitate prescribed home and group training.

Data analysis: Comparisons of the exercise test responses among groups and changes that occurred in the interval of 3 to 26 weeks were performed by analysis of variance. Correlational analysis was used to evaluate the relation between changes in functional capacity and adherence to exercise training. Differences or associations were considered to be significant if p values were <0.05.

Results

Treadmill-induced ischemia and arrhythmia: The overall incidence of treadmill-induced ischemic ST-segment depression of at least 0.1 mV or angina pectoris was 29% (47 of 161 patients) at 3 weeks: 20 patients had angina and ischemic depression, 22 had ischemic depression without angina and 5 had angina without ischemic depression. The frequency of these ischemic abnormalities was not significantly different among groups (Table I). Of the 42 patients with ischemic ST-segment depression of at least 0.1 mV, 10 (24%) manifested "marked" ischemic ST-segment depression of at least 0.2 mV at a heart rate of 135 beats/min or less—a combination that is associated with an increased risk of subsequent cardiac events in patients similar to those in the present study.[3] The overall incidence of treadmill-induced ischemic ST-segment depression of at least 0.1 mV or angina pectoris at 26 weeks was 28% (45 of 160 patients) without significant intergroup differences (Table I).

Treadmill-induced ventricular tachycardia was absent in the 52 patients (32%) who demonstrated treadmill-induced ventricular bigeminy or couplets at 3 weeks. No significant intergroup differences in the frequency of these complex arrhythmias were noted.

Cardiac events: No significant intergroup differences in the rate of cardiac events were noted. Of the 198 training study participants, including 37 control patients who did not undergo 3-week treadmill testing, 28 (14%) experienced cardiac events between 3 and 26 weeks: sudden cardiac death in 2, nonfatal reinfarction in 10, coronary artery bypass surgery in 12, rehospitalization for worsening angina pectoris in 2 and congestive heart failure in 2. Half of these events occurred between 3 and 11 weeks and half between 11 and 26 weeks. Both sudden cardiac deaths (i.e., within 1 hour of the onset of symptoms) occurred between 11 and 26 weeks—1 in a control patient and 1 in a no-training patient. Of the 12 patients who underwent surgery, 3-vessel coronary artery disease was present in 9.

Eight patients refused to continue participation after enrollment in the training study: 2 control patients, 4 no-training and 2 home-training patients. Follow-up to 26 weeks was obtained in all of these patients, 1 of whom underwent coronary artery bypass surgery and 1 experienced nonfatal reinfarction. Two additional patients who moved from the area were lost to follow-up. Thus, of the 198 patients who entered the training study at 3 weeks, 160 (81%) remained in the study at 26 weeks.

Of the 161 patients who underwent treadmill testing at 3 weeks, the incidence of cardiac events 3 to 26 weeks after infarction was significantly greater in those with

TABLE II Peak Functional Capacity After Myocardial Infarction: Maximal METs

	3 Weeks	Δ 3–11 Weeks	Δ 11–26 Weeks	26 Weeks
Home training				
Brief	6.2 ± 1.3	1.5 ± 1.1*	0.2 ± 1.0	8.0 ± 1.5†,‡
Extended	5.8 ± 1.4	1.6 ± 1.2*	0.4 ± 1.1	7.9 ± 1.5†,‡
Group training				
Brief	6.2 ± 1.0	1.4 ± 1.4*	0.2 ± 1.2	7.9 ± 1.3†,‡
Extended	6.6 ± 1.3	1.4 ± 1.3*	0.6 ± 1.1	8.9 ± 1.4†,‡
No-training patients	6.1 ± 1.5	0.8 ± 1.0	0.4 ± 1.0	7.5 ± 1.8
Control patients	—	—	—	7.0 ± 1.7

* $p < 0.05$ vs values in the no-training patients; † $p < 0.05$ vs values in the no-training patients; ‡ $p < 0.001$ vs values in control patients. All values are expressed as mean ± standard deviation. Δ = change in functional capacity; — = not done.

treadmill-induced ischemic ST-segment depression of at least 0.1 mV or angina pectoris than in those without this abnormality: 10 of 47 (22%) vs 11 of 114 (10%) ($p < 0.05$). A substantially higher incidence of subsequent cardiac events was noted in patients with marked ischemic ST-segment depression of at least 0.2 mV at a heart rate of ≤135 beats/min than in those without this combination: 7 of 10 (70%) vs 14 of 151 (9%) ($p < 0.001$).

Adherence to prescribed exercise training: Adherence to home or group training was expressed as the ratio of exercise sessions completed to those prescribed. Adherence between 3 and 11 weeks was 89% for home training and 84% for group training (difference not significant). Adherence between 11 and 26 weeks decreased significantly ($p < 0.05$) to 72 and 71% for home- and group-training groups, respectively.

Nonprescribed physical activity: The total duration of nonprescribed walking per day, from 3 to 26 weeks, was similar for training and no-training patients, (approximately 30 ± 32 min/day) and was slightly higher in control patients (45 ± 44 min/day) (difference not significant). The total amount of more vigorous nonprescribed activity (i.e., 4 METs or more between 3 and 11 weeks) was greater in no-training than in home- or group-training patients: Because of the large inter-individual variation among no-training patients, this difference was not statistically significant (Fig. 2).

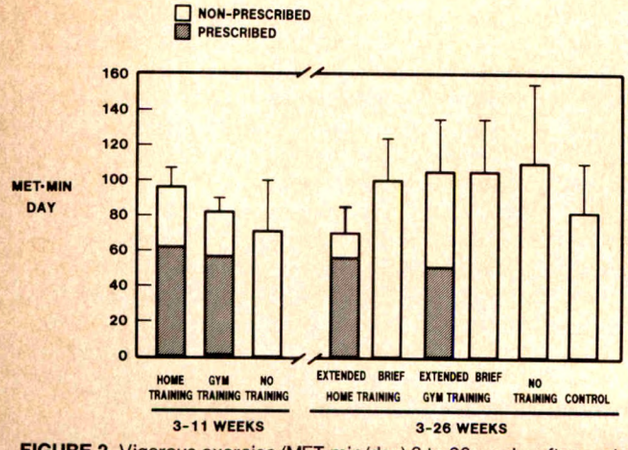

FIGURE 2. Vigorous exercise (MET·min/day) 3 to 26 weeks after acute myocardial infarction (POST-MI). Values are expressed as mean ± standard error of the mean.

Total vigorous exercise: Total vigorous daily exercise, both prescribed and nonprescribed, performed by patients who underwent home or group training between 3 and 11 weeks was not significantly greater than the total of such exercise performed by no-training patients (Fig. 2). No significant intergroup differences in total daily vigorous exercise were noted between 11 and 26 weeks.

Changes in functional capacity 3 to 26 weeks after infarction: The average increase in functional capacity (i.e., peak treadmill workload in METs) between 3 and 26 weeks was significantly greater ($p < 0.05$) in training groups than in the no-training groups (1.8 vs 1.2 METs, respectively) (Table II). Most of this increase occurred between 3 and 11 weeks. Overall, home- and group-training patients demonstrated a 35% increase in functional capacity between 3 and 26 weeks, compared with 23% for no-training patients.

Exercise-induced abnormalities during home training: Of the 66 patients who began home training, 20 demonstrated ventricular arrhythmias on the brief telephone transmissions: isolated premature ventricular contractions in 14, bigeminy in 5 and couplets in 1. Antiarrhythmic therapy was instituted in the patient with couplets and in 1 of the patients with bigeminy. No patient with exercise-induced premature ventricular contractions was withdrawn from the study and none experienced cardiac events.

Exercise-induced ischemic ST-segment depression less than 0.2 mV was observed in 4 patients, all of whom had demonstrated at least 0.1 mV of treadmill-induced ischemic ST-segment depression at 3 weeks. No patient was withdrawn from the study solely because of exercise-induced ischemic ST-segment depression. Three patients who experienced an increasing frequency or intensity of anginal symptoms between 3 and 26 weeks were referred to their physicians by the nurse for further evaluation. At 3 weeks, all 3 patients had demonstrated mild treadmill angina and marked ischemic ST-segment depression as previously defined. Two patients underwent coronary artery surgery and 1 resumed exercise training after treatment with β-blocking drugs.

Exercise-induced abnormalities detected during group training: Of the 61 patients who commenced group training, 2 were referred to their physicians for

antiarrhythmic therapy on the basis of episodes of bigeminy and couplets recorded during exercise sessions; palpitation prompted brief transthoracic electrocardiographic monitoring through defibrillator paddles. Palpitation was unaccompanied by chest pain or dizziness and both patients resumed exercise training. No patient was referred to his physician because of increasing episodes of angina during the training sessions and no patient was withdrawn from the study for this reason.

Discussion

The medically directed at-home rehabilitation program described here represents a new model for augmenting the functional capacity of low-risk patients at a time when physician and patient alike share a concern that physical activity may precipitate subsequent cardiac events. The low rate of cardiac events observed in the present study (1% mortality, 6% combined death and reinfarction and 14% total events) reflects, in part, the identification of a low-risk population by means of historical and clinical characteristics and treadmill exercise testing.[3] The 203 patients who were considered eligible for symptom-limited treadmill testing 3 weeks after myocardial infarction represent 54% of the total population.

Since subsequent cardiac events occurred in 4 of the 5 patients who were excluded from the training study because of severe treadmill-induced angina or heart failure, this exclusion seems appropriate. Of the 161 men who were entered into the training study after 3-week treadmill testing, 10 had prognostically important ischemic ST-segment depression (0.2 mV or greater at a heart rate of ≤135 beats/min,[3] 7 of whom experienced subsequent cardiac events: rehospitalization for increasingly severe angina pectoris in 5 and nonfatal reinfarction in 2. Thus, of the 166 men who underwent treadmill testing, including the 5 who were excluded from the training study, 25 experienced subsequent cardiac events, 11 (44%) of whom demonstrated severe abnormalities during treadmill testing. Prompt cardiac catheterization and consideration of coronary artery surgery may be appropriate in patients with severe treadmill-induced ischemic abnormalities.

In patients with less severe ischemia on treadmill testing at 3 weeks, continued surveillance provides an alternative to immediate cardiac catheterization: Among patients without severe angina or "high-risk" ischemic ST-segment depression during treadmill testing, the incidence of cardiac events was low (3 of 37, or 8%). None of these cardiac events was fatal.

Participation in home training resulted in more intensive medical surveillance than is standard in most communities. Patients in the present study visited their physicians an average of twice in the first 11 weeks and once thereafter. In contrast, telephone contact, including brief exercise electrocardiographic transmissions, occurred 16 and 46 times, respectively, in patients completing brief and extended home training. The extended surveillance provided by the nurse's frequent telephone contact with the patient may have contributed to the low rate of cardiac events observed in patients who underwent home training. The 3 patients who reported an increasing frequency or intensity of anginal symptoms during the telephone contacts were referred to their physicians for further evaluation. The ease of communication afforded by regular contact appeared to facilitate patients' reports of a change in their pattern of chest pain. No patient who died suddenly had an opportunity to receive prolonged surveillance.

The risk of exercise-induced cardiac arrest in patients with ischemic heart disease is related to the intensity of exercise training. Most such episodes occur at heart rates exceeding the prescribed range.[11] Maintaining the training heart rate within the prescribed range during home exercise was reliably accomplished by the use of portable monitors that alerted patients to excessive heart rates. The intensity of exercise training between 3 and 11 weeks, as judged from the training heart rate range of 96 to 121 beats/min, was somewhat lower than the rate generally used for exercise training in patients with chronic ischemic heart disease.[12] Despite this, patients who underwent home or group training demonstrated a 50% greater increase in functional capacity between 3 and 26 weeks than was observed in the no-training patients: 1.8 vs 1.2 METs ($p < 0.05$); most of this increase occurred by 11 weeks.

This comparison underestimates the impact of prescribed exercise training on functional capacity, for the no-training patients were unexpectedly active, especially in the early recovery period 3 to 11 weeks after AMI. Through exercise testing and the counseling that followed, these patients received substantial reassurance concerning their ability to resume their customary activities with safety. The total amount of daily vigorous nonprescribed exercise performed 3 to 11 weeks after AMI was slightly greater in the no-training patients than in those who underwent training and was not significantly less than the total amount of prescribed and nonprescribed physical activity performed by patients at home or in group training. The present study corroborates earlier observations from this laboratory that treadmill testing followed by a thorough explanation of exercise test results tends to enhance physical activity in the early period after clinically uncomplicated AMI.[13] At 26 weeks the peak functional capacity of control patients, who had no exercise testing, counseling or prescribed exercise was 1 to 2 METs lower than that of patients who underwent training ($p < 0.001$).

It is reasonable to ask whether the relatively small absolute difference in functional capacity between training and no-training patients justifies the elaborate program of surveillance and monitoring that was undertaken. The absence of training-related complications makes many of the precautions of home training seem unwarranted in hindsight. However, the present study was concerned not only with safety but with patient satisfaction.

Patient satisfaction was closely related to the extent of contact with the professional staff, especially the nurse. The 95% rate of enrollment of medically eligible

patients (175 of 185) far exceeds that observed in community rehabilitation programs, and obviates 1 of the major problems in research in rehabilitation after AMI (i.e., a selection bias favoring more highly motivated patients). The 71% or greater level of adherence to prescribed exercise training noted in this study, even between 11 and 26 weeks, is far greater than that reported in most previous studies of training after AMI.[14,15] Finally, the rate of refusal to continue further in the training study was substantially lower in training than in no-training or control patients. Of the 8 patient refusals, 6 occurred in the no-training and control patients: 4 in the former and 2 in the latter. The support and encouragment provided by the nurse appeared to contribute to the high rate of adherence and low rate of refusal in patients who underwent home and group training. Patients who participated in home training enjoyed continuing contact with the same nurse who participated in the initial exercise testing and counseling. This afforded an opportunity for patients to receive further information about their condition, ongoing encouragement of exercise training and risk factor modification, and ready access to the medical system in case of a change in clinical status.

Group rehabilitation programs offer not only augmentation of functional capacity, but enhancement of psychologic status,[16] and help in controlling risk factors such as smoking[17] and hyperlipidemia.[18] However, except for peer support and immediately available cardiac resuscitation, these services are also effectively provided in the context of at-home rehabilitation.[19–21] At-home rehabilitation incorporating frequent contact with medical personnel appears to be a feasible alternative to group exercise-training programs for clinically low-risk patients after AMI. Patients with more severe clinical manifestations of disease may require on-site medical supervision of exercise training.

Medically directed at-home rehabilitation has the potential to increase the convenience and availability of rehabilitative services for patients after AMI. Many patients choose not to enroll in group programs for personal or financial reasons, and others quickly drop out because of the inconvenience of commuting to a group training facility.[15,22] Patients who underwent group training spent an average of 100 min/week in transit to and from the exercise facility—an amount that approximated the time spent by patients within the prescribed training range at home. Moreover, access to medically supervised group programs tends to be limited to larger communities.

The at-home rehabilitation program described here should be considered a research prototype, which was designed to safeguard patient safety and to assure adherence and physiologic efficacy. Simplifying the regimen may assure its clinical efficacy without compromising its safety. Further research is required to determine which form of at-home rehabilitation is most cost-effective. Three months of at-home rehabilitation using the equipment and methods described in this study could be offered for little more than $300 per patient (see Appendix)—an amount that many patients may be willing to pay out of pocket if necessary.

The present study suggests that nearly half of the 600,000 Americans who survive an AMI each year may be capable of safely completing 3 months of at-home rehabilitation—nearly 3 times the number of patients after AMI currently undergoing rehabilitation in group programs.

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Appendix

Comparative costs of group and at-home rehabilitation programs: The median cost per session of medically supervised group exercise programs during the first 12 weeks of participation is $20.00 (range $9.00 to $69.00). The cost of 12 weeks' participation in such programs (36 sessions) approximates $720.00.

The projected cost of medically directed at-home rehabilitation depends on whether patients purchase or lease the equipment. The following estimates reflect the cost of leasing the exercise cycles and monitoring equipment assuming an average life of 2 years for the equipment. Eighty patients participating for a period of 12 weeks during 1 year would require 20 sets of equipment, 8 to 10% of a physician's time and 30% of a registered nurse's time, trained in cardiac rehabilitation. The cost of 12 weeks' participation approximates $328.00. This cost assumes that the at-home program uses office facilities already dedicated to a similar purpose, such as medically supervised exercise training in YMCA programs.

Costs for 160 Patients Over Two Years

Equipment	Cost ($)
ExerSentry monitors (20 × $110)	2,200
Cardiobeeper monitors (20 × $350)	7,000
Cardiobeeper decodalyzer	1,500
Schwinn XR7 stationary cycles (20 × $250)	5,000
Equipment maintenance ($1,000/year)	2,000
ECG supplies (160 × $5)	800
Telephone costs ($1/call, 12 calls × 160 pts)	1,920
Subtotal	20,420
Cardiology consultation (2 hrs/pt × 160 pts) 8% FTE $12,000 (2 years)	
Registered nurse (at $30,000/year)	
Counseling (3 hrs/pt × 160 = 480 hrs)	5 hrs/wk
Patient phone contact (12 calls × 12 min, each × 160 = 368 hrs)	4 hrs/wk
Records management	
13 hrs/wk = 33% FTE	
= $20,000 (2 yrs)	
Total $52,420	
= $328/patient	

FTE = full-time equivalent.

Effect of Beta-Adrenergic Blockade on the Results of Exercise Testing Related to the Extent of Coronary Artery Disease

STEPHEN W.-C. HO, MBBS, FRACP, MICHAEL J. McCOMISH, MBBS, FRACP, and ROGER R. TAYLOR, MBBS, FRACP

Maximal treadmill testing was carried out in 50 patients with angiographically documented coronary artery disease (CAD) in the presence and absence of β-adrenoceptor blockade. The results were related to the extent of CAD and interpreted relative to the clinical value of exercise testing. Maximal heart rate and systolic blood pressure were significantly lower during treatment with β-blocking drugs. The average exercise duration was 1.3 ± 1.9 minutes greater (± standard deviation), regardless of coronary anatomy. Of the 20 subjects with 3-vessel or left main CAD (severe CAD), 8 patients completed 3 stages (9 minutes) of exercise during treatment; only 4 did so without treatment. Angina was significantly more often the limiting symptom with severe CAD, and this association was abolished by β blockade; 1 of 20 with severe CAD completed 3 stages of exercise and was not limited by angina without β-blocking treatment, whereas 7 had these features during β-blockade therapy. Maximal ST-segment depression was not related to the extent of CAD with or without therapy. Beta blockade suppressed the occurrence of ST depression, or delayed its appearance by an average of 2.0 ± 2.3 minutes and reduced its severity by 0.5 ± 0.9 mm. All tests in which ST depression was completely suppressed were associated with inadequate heart rate response, regarded as diagnostically inconclusive rather than negative. However, during β-blocking treatment, 14 tests (28%) were inconclusive, which, in routine practice, would have necessitated repeat testing. It is concluded that β blockade significantly obscures the diagnostic interpretation of exercise testing and impairs the ability to select subjects likely to have extensive CAD. **(Am J Cardiol 1985;55:258–262)**

The usefulness and limitations of exercise testing are well documented in the diagnosis of myocardial ischemia,[1,2] in predicting the extent of atherosclerotic coronary artery disease (CAD)[2–6] and in selecting high- and low-risk patient groups with CAD.[7–13] Beta-adrenoceptor blocking drugs can delay the onset of angina[14–20] and reduce or delay exercise-induced ST-segment changes,[15,16,21–23] and consequently, many physicians avoid prescribing them before assessing patients by exercise testing. However, some physicians are reluctant to stop therapy in referred patients because of a possible rebound effect.[24] The need to stop therapy for diagnostic testing has been questioned; some believe that the sensitivity of testing, reflected by ST-segment changes, is not impaired.[23] Further, exercise testing is being used increasingly to select for angiography those more likely to have extensive CAD and those with a worse prognosis who may benefit from surgery.[25,26] The purpose of this study was to determine if β-blocker therapy obscures the selection of patients with extensive CAD, to examine how this therapy affects the numerous variables assessed at exercise testing, and to determine if its effects vary with the extent of CAD.

From the Departments of Cardiology and Medicine, Royal Perth Hospital, Perth, Western Australia. Manuscript received June 25, 1984; revised manuscript received October 23, 1984, accepted October 24, 1984.

Address for reprints: Professor R. R. Taylor, Professor of Cardiology, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia 6001.

Methods

Patients with angina referred to coronary angiography to evaluate the possibility of surgery were exercised during treatment with β-blocking drugs and without such treatment. Subjects in stable sinus rhythm at rest in whom at least 1 major coronary artery had a 50% reduction in average luminal diameter were included. Some subjects were already receiving treatment and were included in the study if they were receiving metoprolol, 100 mg or atenolol, 50 mg twice daily, propranolol, 40 mg 3 times daily, pindolol 5 mg 4 times daily, or a regimen that produced 20% decrease in heart rate at rest compared with the period without treatment. Exclusion criteria were myocardial infarction within 6 weeks, previous coronary artery bypass surgery or angioplasty, valvular heart

disease, severe hypertension, congestive heart failure, concurrent therapy with digitalis or calcium channel–blocking drugs or electrocardiographic changes at rest (ST-segment depression or bundle branch block) that interfered with test interpretation.

Fifty subjects (47 men, 3 women), aged 33 to 70 years (mean 54 ± 9 [± standard deviation]) were studied, with and without treatment with metoprolol (32 subjects), propranolol (12), atenolol (5), or pindolol (1). The only other drugs being taken were mexiletine, quinidine bisulphate and prazosin each in 1 subject, a thiazide diuretic in 2 and isosorbide nitrate. With the exception of the β-blocking drug, treatment remained unchanged between the 2 exercise tests.

Symptom-limited graded treadmill testing was performed according to the Bruce protocol,[1] commencing in stage 1, at least 2 hours after food, and without knowledge of the coronary angiographic findings. In 25 subjects an exercise test was performed first during β-blocking therapy and a second test after such treatment had been withheld for 48 to 72 hours. The reverse sequence applied to the other 25 patients. Maximal tolerated exercise was undertaken to an endpoint of increasing angina, exhaustion, dyspnea, or, in 1 subject, ventricular tachycardia. A decrease in systolic blood pressure, seen in 3 subjects, did not constitute an endpoint. Heart rate and leads V_5 and modified II of the electrocardiogram were monitored and were recorded (Avionics equipment) at the onset of ST-segment changes and of chest pain, at the end of each stage, at the termination of the test and thereafter at 1-minute intervals until return of the heart rate to 90 beats/min or until disappearance of exercise-induced electrocardiographic changes. Cuff measurements of blood pressure were made at the end of each stage.

The electrocardiographic tracings were analyzed independently by another observer. ST-segment changes were classified according to the criteria proposed by Goldschlager et al[3]: type 1A—at least 1 mm of J-point depression with a downsloping ST segment; type 1B—at least 1 mm of J depression with a horizontal ST segment; type 2—upsloping ST segment that remained depressed at least 1.5 mm at 80 ms after the J point. If less, or no, ST-segment change occurred, the test was defined as negative if the target heart rate—90% of the predicted maximal rate—had been attained but as inconclusive if the target heart rate was not reached.

The results of selective coronary angiography and left ventriculography were analyzed by a third observer without knowledge of the patients' clinical or exercise data. Narrowing of the average luminal diameter of a coronary vessel in multiple views of 50% of more was considered significant. The extent of obstructive disease was characterized as 1-, 2- or 3-vessel, with or without left main (LM) disease, and was also assessed according to the system of Brandt et al.[27] This takes account of the severity of coronary obstructions and the amount of myocardium supplied by obstructed arteries in order to obtain a myocardial score. In the 48 subjects in whom left ventriculography was performed, left ventricular (LV) function was assessed visually and graded subjectively into 2 groups, normal or mildly depressed and moderately or severely depressed.

Group mean results were compared by the Student t test and differences with and without β-blocking therapy were compared using a Student t test for paired data. Comparisons of proportions in different groups were tested by chi-square analysis applying the Yates correction.

Results

One-vessel CAD was present in 14 subjects; the disease involved the left anterior descending coronary artery (LAD) in 8, left circumflex artery in 3 and the right coronary artery in 3 patients. Two-vessel CAD was present in 16 subjects, 4 of whom had proximal LAD involvement. Fifteen patients had 3-vessel CAD; 5 had LM obstruction, 4 of whom had proximal LAD obstruction and 1 of whom had 3-vessel CAD (4 of the 5 had exercise testing before the demonstration of LM obstruction). LV function was normal or mildly depressed in 38 and moderately or severely depressed in 10.

Maximal heart rate and blood pressure: The maximal heart rate with exercise averaged 141 ± 22 beats/min in the absence of β blockade and 113 ± 18 beats/min with β blockade ($p < 0.001$). The rate achieved was not related to the extent of CAD; without β blockade the average heart rate in those with LM CAD was 138 beats/min and in the others it was 141 beats/min. Peak systolic blood pressure attained was 19 ± 21 mm Hg less during β-blocker therapy ($p < 0.001$).

Duration of exercise: The average exercise duration in the 50 subjects was 7.3 ± 2.9 minutes without β-blocking treatment and 8.6 ± 2.6 minutes with β blockade. The 5 subjects with LM CAD had a significantly lower exercise duration than the remainder only when untreated (Fig. 1). Otherwise, those with 1-, 2- and 3-vessel CAD did not have different levels of exercise tolerance. Higher myocardial score tended to be associated with shorter duration of exercise, but had a weak relationship both with and without therapy ($r = -0.24$ and -0.26, respectively, $0.05 < p < 0.1$).

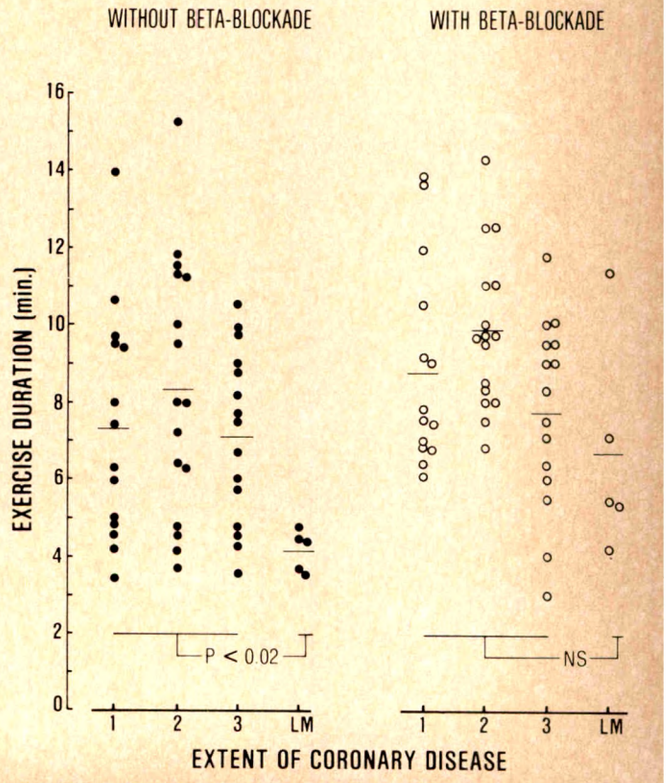

FIGURE 1. Duration of maximal exercise related to the extent of coronary disease. The duration was significantly less in those with left main (LM) disease only in the absence of β blockade. NS = not significant.

Exercise duration averaged 1.3 ± 1.9 minutes more with β blockade than without ($p < 0.001$). The difference was not related to coronary anatomy (Fig. 2), myocardial score or LV function. The difference in exercise duration between the 2 tests was, however, related to the limiting symptom in the absence of β-blocking drug therapy. Beta blockade actually decreased exercise tolerance in 9 of 19 patients limited by fatigue/breathlessness, compared with only 5 of 30 limited by angina ($p < 0.05$).

Four subjects with 3-vessel or LM CAD (severe CAD) completed stage 3 of the Bruce protocol when exercised without β-blocker therapy, whereas with β-blocker therapy, 5 others in addition to 3 of these 4 completed stage 3.

Occurrence of angina and angina as the limiting symptom: During exercise testing without β-blocking treatment, 11 subjects had no angina and angina did not develop when they received therapy. Of the 39 patients in whom angina developed in the absence of β-blocking treatment, 9 did not do so with therapy, and the time of onset of angina was significantly delayed in the other 30, averaging 6.8 ± 2.3 minutes during therapy and 5.7 ± 2.3 minutes without therapy ($p < 0.01$).

In the absence of β-blocking drug treatment, 30 subjects were limited by angina and 20 were not (19 limited by exhaustion/dyspnea and 1 patient by ventricular tachycardia), while during therapy 17 were limited by angina and 33 by exhaustion/dyspnea ($p < 0.02$). Without β-blocking treatment the nature of the limiting symptom was related to the extent of CAD and to the myocardial score. Severe CAD was present in 17 of 30 patients limited by angina, but in only 3 of the 20 patients not limited by angina ($p < 0.01$) (Fig. 3, top).

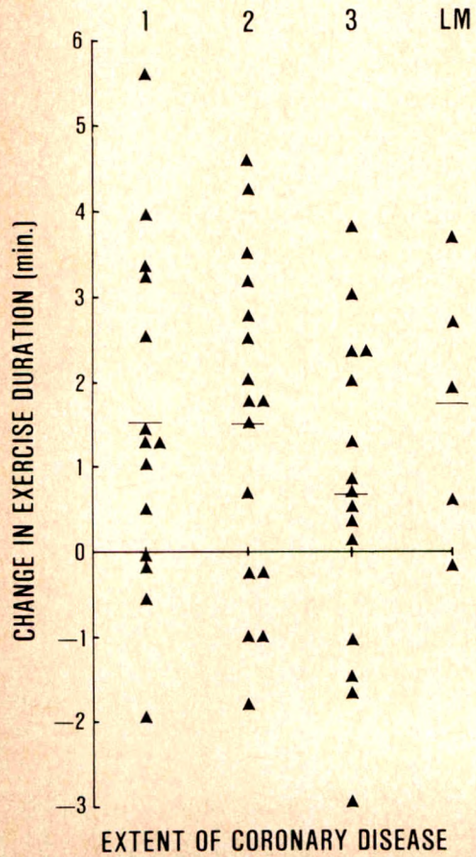

FIGURE 2. The change in duration of exercise with β blockade bears no relation to the extent of coronary disease. LM = left main.

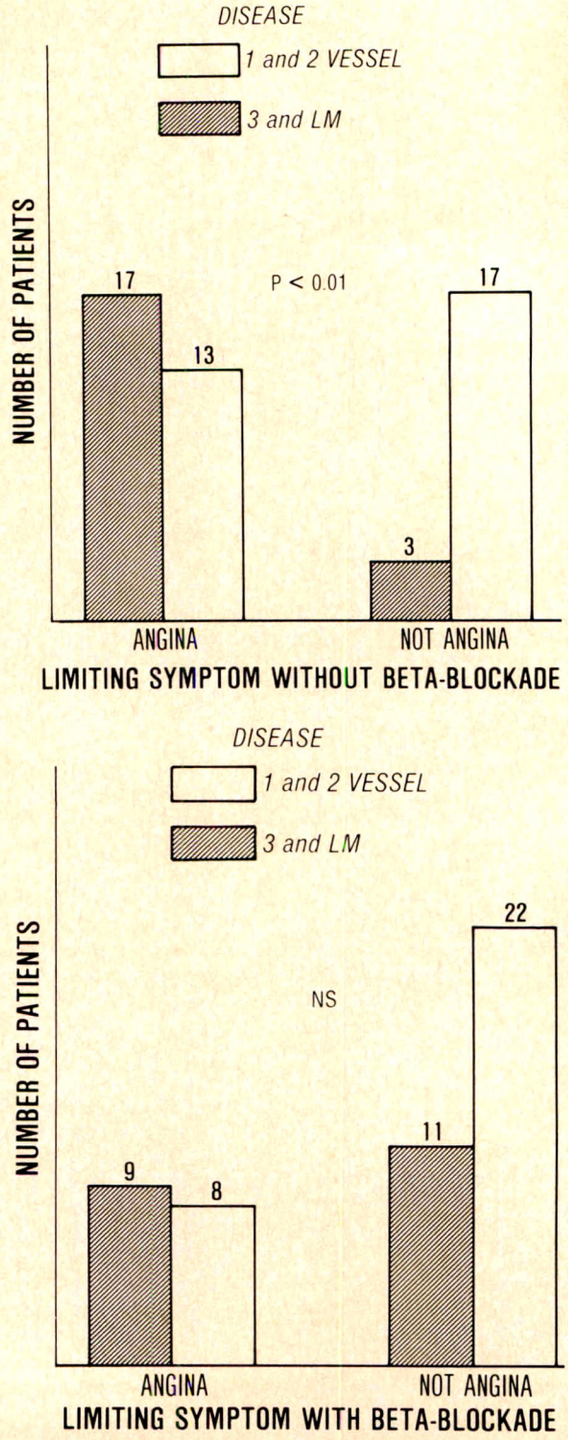

FIGURE 3. When angina was not the limiting symptom, 3-vessel or left main (LM) disease was uncommon in the absence of β blockade (**top**), but this was not so in the presence of β blockade (**bottom**). NS = not significant.

The myocardial score was 8.0 ± 2.4 in the patients limited by angina and 5.7 ± 2.5 in those not limited by angina ($p < 0.01$).

The relation between the limiting symptom of angina and the severity of CAD was abolished by treatment with β-blocking drugs (Fig. 3, bottom). Four of the 5 patients with LM CAD were limited by angina without treatment but only 1 patient was so limited with treatment. The change in the limiting symptom produced by β-blocking treatment was not related to LV function, and limitation by exhaustion/dyspnea was not associated with poor LV function assessed at angiography. In fact, 8 of the 10 subjects with moderate or severe depression of LV function were limited by angina when not receiving β-blocking therapy.

ST-segment changes: In the absence of β blockade, 3 subjects had negative test responses in terms of ST-segment depression, and 8 had inconclusive results. The inconclusive test results included only 1 subject with 3-vessel CAD; all others with severe CAD had ST-segment depression. Those with ST changes also had higher myocardial scores than those without (7.8 ± 2.5 vs 4.6 ± 1.8, $p < 0.001$). However, among those with ST depression, neither the magnitude nor the grading related to the extent of CAD; those with severe and mild disease had similar average ST depression, and no single level of ST depression, such as 2 or 3 mm, was associated with a greater proportion of patients with severe CAD.

Figure 4 shows how β-blocker treatment affected ST-segment grading. In 24 subjects the ST grade was unchanged between tests: 13 with grade 1A ST changes, 2 with grade 1B, and 2 with grade 2; in 1 patient the results were negative and in 6 the results were inconclusive on both tests. The grade was decreased by β-blocking treatment in 19 patients and it was increased in 7 patients; the changes were unrelated to coronary anatomy, myocardial score or LV function. Six patients with positive test responses without treatment had inconclusive responses during treatment; 1 of these patients had 3-vessel and 1 LM CAD. However, no test response changed to negative. Fourteen patients had inconclusive test responses during treatment; 2 of these patients had 3-vessel and 1 had LM CAD.

The onset of ST depression in those in whom it occurred in both tests was delayed an average of 2.0 ± 2.3 min ($p < 0.001$), without relation to the extent of CAD. Beta blockade decreased the maximal ST depression by an average of 0.5 ± 0.9 mm ($p < 0.01$), although in 8 patients an increase in ST depression occurred that was associated with a longer duration of exercise. The magnitude of the change was not related to the extent of CAD, but had a direct linear relation to the absolute magnitude of ST depression without β blockade ($p < 0.001$); that is, a proportionate reduction in ST depression tended to be produced.

Discussion

The increase in exercise tolerance with β-blocking treatment usually described in patients with CAD is, in fact, a delayed onset of angina in a submaximal test.[14,15,17–20] Our results agree that angina may be delayed or abolished.[14,19,22] The duration of maximal tolerated exercise increased, agreeing with some study results[16] but not with others.[28] Maximal exercise tolerance undoubtedly may decrease in the normal subject.[29] Our conclusions are relevant to the exercise testing of subjects with probable or established CAD, although the detailed results pertain to the group studied.

The object was to determine how β blockade influences exercise test variables that have diagnostic or prognostic value. The duration of maximal exercise is one of the best guides to prognosis in patients with CAD.[2,8–13] Those with a good exercise tolerance have a good prognosis, even among subjects with a markedly positive test in terms of ST-segment change[10,11] or in patients with 3-vessel CAD.[13] Ability to complete stage 3 of the Bruce protocol is associated with a good prognosis and a low incidence of LM or 3-vessel CAD.[2,8–13] In our study, in the absence of β blockade, 4 of 20 subjects with 3-vessel or LM CAD completed stage 3 of the Bruce protocol; during β-blocking treatment, 8 did so. Of course, we did not address the possibility that the improvement in exercise tolerance with β-blocking drug treatment may be accompanied by an appropriate improvement in prognosis.

The association of angina as the limiting symptom with the extent of CAD may explain the additional prognostic significance some have found associated with the occurrence of angina during exercise testing, even in those with known CAD.[2,7] Beta-blocking drug treatment tended to convert the limiting symptom from angina, especially in those with extensive CAD. Without β-blocking treatment, all but 3 of the 20 with severe CAD were limited by angina but during treatment only 9 were so limited. The absence of angina as the limiting symptom, coupled with the ability to complete 9 minutes of exercise, was seen in only 1 patient in this category without treatment, but both of these features were present in 7 during treatment. Hence, consideration of

OFF / ON	1A	1B	2	N	I
1A	13	0	1	0	1
1B	5	2	4	0	1
2	3	3	2	0	0
N	0	0	0	1	0
I	2	3	1	2	6

FIGURE 4. Classification of ST-segment depression with (on) and without (off) β blockade. The numbers of subjects with a given ST grade without β blockade are read in the **vertical columns** and the numbers on β-blockade in the **horizontal columns.** I = inconclusive; N = negative. See text for description.

the limiting symptom and the duration of exercise together would allow reasonable exclusion of severe CAD only in the absence of β-blocking drug treatment.

Disagreement exists concerning the effect of β blockade on exercise-induced ST-segment changes. The consensus is that the onset of ST-segment depression is delayed,[15,21] as we found. However, some investigators have found the ST-segment depression occurring during testing is decreased[15,16,22,23]; others have found that it did not change.[18,21] Exercise in some of these studies was submaximal,[15,16,18,22] so that the reported ST-segment depression was that occurring at the onset of angina or corresponding endpoint. How this is affected is not really germane to maximal exercise testing, for either diagnostic or prognostic purposes. We found that ST-segment depression at maximal exercise decreased, consistent with some observations[16,23,30] but not others.[21] Recent studies support the prognostic value of ST-segment depression,[13] which is influenced by β blockade, although the predictive value of marked changes per se may be less than formerly believed.[10,11] We found no relation between the extent of ST depression and the extent of CAD even in the absence of β blockade.

From the diagnostic viewpoint, in terms of ST-segment change, some have considered that β blockade reduces the incidence of false-positive test responses without increasing the incidence of false-negative responses.[23] Although none of our positive test results were converted to strictly negative results, 6 were converted to inconclusive tests that would have been classified as negative by Marcomichelakis et al.[23] The idea of a target heart rate during β-blocker therapy may be questioned but, in practice, the absence of ST changes can hardly be regarded as a negative response when heart rate is not adequately raised. When these additional 6 inconclusive results are added to the others, there were a total of 14 inconclusive tests during treatment. Hence, if our subjects had undergone exercise testing for diagnostic purposes while receiving β-blocker therapy, 28% of the tests should have been repeated without treatment.

Kardash et al[20] described a different approach to analyzing ST-segment changes by relating the progressive ST changes throughout exercise to concurrent heart rate changes, obtaining an ST/HR regression. Excellent agreement was found between the results and the extent of CAD, even in the presence of β blockade.[20] Kardash et al monitored 13 leads, but the analysis is also critically dependent upon minute fractional measurement of ST depression, the practicality of which is questionable.

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Early Exercise Training in Patients Older than Age 65 Years Compared with that in Younger Patients After Acute Myocardial Infarction or Coronary Artery Bypass Grafting

MARK A. WILLIAMS, PhD, CARL M. MARESH, PhD, DENNIS J. ESTERBROOKS, MD, JAMES J. HARBRECHT, MD, and MICHAEL H. SKETCH, MD

To evaluate potential benefits that elderly cardiac patients might gain from early exercise programs, 361 such patients were studied: group I—60 patients aged 44 years or younger; group II—114 patients aged 45 to 54 years; group III—111 patients aged 55 to 64 years; and group IV—76 elderly patients aged 65 years or older. All patients participated in a 12-week exercise program within 6 weeks of acute myocardial infarction or coronary artery bypass grafting. All patients performed symptom-limited exercise tests before and after completion of the exercise program. Between tests, elderly patients manifested significant differences in body weight (76.9 to 75.2 kg), percent body fat (22.3 to 20.8 kg), heart rate at rest (77 to 68 beats/min), maximal heart rate (126 to 138 beats/min), maximal METs (5.3 to 8.1), submaximal average double product (17,305 to 14,071), and submaximal average rating of perceived exertion (12 to 10 [$p < 0.05$]). Magnitudes of change were similar among groups, although the elderly patient group had a significantly lower absolute physical work capacity at testing after training than the other 3 groups ($p < 0.05$). In the 25 elderly patients who received β-blocking drugs, METs increased from 5.1 to 7.8 ($p < 0.05$). In the remaining 51 elderly patients not receiving β-blocking drugs, METs increased from 5.4 to 8.2 ($p < 0.05$). The magnitude of increase in patients who received β-blocking drugs was not significantly different from that in patients not receiving β-blocking drugs. Results suggest that benefits of early exercise programs seen in young cardiac patients may also be expected in elderly cardiac patients. (Am J Cardiol 1985;55:263–266)

The benefits of exercise training as part of the rehabilitation of cardiac patients have been described by previous investigators. Improvement in the hemodynamic responses to exercise,[1–3] physical work capacity[4–6] and cardiac function[7–9] have been described. Potential improvements in morbidity, mortality[10–12] and pyschologic responses to heart disease[13,14] have also been described. Typically, the subjects who participated in these studies had had acute myocardial infarction (AMI) or had undergone coronary artery bypass grafting (CABG) from the ages of 45 to 65 years. To our knowledge, the benefits of exercise training in elderly cardiac patients have not been described. Therefore, in this study, we evaluated the results achieved from exercise training in 76 elderly cardiac patients and compared the data with those obtained from 285 subgrouped, younger cardiac patients.

From the Cardiology Division, Creighton University Medical School, Omaha, Nebraska; the Health Institute, St. Luke's Hospital, Kansas City, Missouri; and the Midwest Research Institute, Kansas City, Missouri. Manuscript received August 16, 1984; revised manuscript received October 26, 1984, accepted October 29, 1984.

Address for reprints: Mark A. Williams, PhD, Cardiac Center, Creighton University, 601 North 30th Street, Omaha, Nebraska 68131.

Methods

To provide adequate patient numbers for evaluation, a collaborative investigation that involved the outpatient cardiac rehabilitation exercise programs of Creighton University/St. Joseph Hospital, Omaha, Nebraska, and St. Luke's Hospital, Kansas City, Missouri, was undertaken. Standard criteria for the exclusion of patients from cardiac exercise training were used.[15] Both programs had similar protocols of patient evaluation and exercise training. Three hundred sixty-one men, 166 after myocardial infarction and 195 after CABG, were studied. Ninety-three of the 195 CABG patients (48%) had histories of myocardial infarction. All patients began the exercise training program within 6 weeks (mean 4.5) of AMI or CABG. Patients were instructed to continue taking all prescribed medications before testing and during the exercise program. Subjects were classified into 4 groups according to age. Group I patients (n = 60) were 44 years or younger (mean 40 ± 4); group II patients (n = 114) were 45 to 54 years (mean 50 ± 3); group III patients (n = 111) were 55

TABLE I Results of the Evaluation of Elderly Patients Before and After Training (Group IV, Mean Age 70.2 ± 3.2 Years)

	Before Training	After Training
Body weight (kg)	76.9 ± 12.2	75.2 ± 11.9*
Body fat (%)	22.3 ± 5.7	20.8 ± 5.4*
Vital capacity (liters) (n = 34)	3.6 ± 0.6	3.6 ± 0.5
FEV_1 (% of vital capacity) (n = 34)	73.9 ± 12.1	79.4 ± 7.4*
Before exercise		
HR (beats/min)	77 ± 14	68 ± 9*
Systolic BP (mm Hg)	125 ± 21	122 ± 19
Diastolic BP (mm Hg)	76 ± 10	73 ± 9
Maximal exercise		
HR	126 ± 20	138 ± 20*
Systolic BP	161 ± 27	171 ± 24*
HR × BP × 10^{-2}	205 ± 55	234 ± 48*
Physical work capacity (METs)	5.3 ± 1.3	8.1 ± 1.6*
Submaximal exercise		
Average HR × BP × 10^{-2} (submaximal)	173 ± 44	141 ± 35*
Average RPE (submaximal)	12 ± 2	10 ± 2*

* $p < 0.05$.
BP = blood pressure; FEV_1 = forced expiratory ventilation in 1 second; HR = heart rate; HR × BP = heart rate × systolic blood pressure; RPE = rating of perceived exertion.

to 64 years (mean 59 ± 3); and group IV patients (n = 76) were 65 to 82 years (mean 70 ± 3).

Before and after the exercise training program, all patients received an evaluation that included a continuous, multistage treadmill test performed until onset of contraindicating signs, symptoms or fatigue (72% fatigue, 11% complex ventricular arrhythmias, 10% angina and 7% ST-segment depression). The protocol allowed for increases in work of 1 MET per stage.[16] Treadmills were regularly calibrated and patients were instructed not to hold onto the handrails of the treadmill. Standard 12-lead electrocardiograms were obtained from each patient at rest in both the supine and standing positions, during the last 15 seconds of each exercise stage, immediately on cessation of exercise while standing, and at minutes 1 through 6 of supine or seated recovery. Data collected from the exercise tests included heart rate (HR) and blood pressure (BP) at rest, exercise HR and BP, exercise HR-BP product, estimation of the patient's physical work capacity in METs and ratings of perceived exertion.[17] The average values of actual HB-BP products and ratings of perceived exertion were calculated from comparable submaximal treadmill stages.[18]

The percentage of body fat was estimated using a skinfold measurement technique.[19] Pulmonary function studies (vital capacity and forced expiratory volume in 1 second) were obtained in 34 of the 76 elderly patients.

Before participating in the study protocol, each patient signed an informed consent for participation. After initial evaluation, each patient entered a 12-week exercise program that consisted of 40 minutes of circuit-station training using alternating arm and leg exercise 3 days/week. During the exercise sessions, the electrocardiograms of all patients were continuously monitored using a single bipolar lead, hardwire or telemetry, central station monitoring system. Hard copy printouts were periodically recorded. The intensity of exercise training resulted in HR that ranged between 70 and 85% of the maximal HR attained during symptom-limited exercise testing. Exercise heart rates were maintained within 5 beats of each patient's HR prescription.

Statistical analysis was accomplished using an IBM systems 4341 computer and programs from the statistical package for social sciences (SPSS).[20] Data were analyzed using a Student

TABLE II Results of Exercise Tests Before and After Training in Elderly Patients

	Before Training	After Training
After AMI (n = 41)		
Physical work capacity (METs)	5.4 ± 1.3	8.0 ± 1.4*
Average HR × BP × 10^{-2} (submaximal)	168 ± 43	135 ± 33*
Average RPE (submaximal)	13 ± 2	11 ± 2*
After CABG (n = 35)		
Physical work capacity (METs)	5.1 ± 1.3	8.1 ± 1.8*
Average HR × BP × 10^{-2} (submaximal)	179 ± 44	148 ± 36*
Average RPE (submaximal)	12 ± 2	10 ± 2*

* $p < 0.05$.
AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; other abbreviations as in Table I.

t test for both correlated means and noncorrelated means. A p value of less than 0.05 was considered significant when comparing groups of means.

Results

Overall program attendance was 85% (range 44 to 100%). Attendance among the elderly patient group was 90%. No patient experienced an untoward event during either exercise testing or training.

The results of the evaluations in the elderly patients and selected subgroups before and after training are listed in Tables I to III. After training, as a group, elderly patients showed significant decreases in body weight and percentage of body fat ($p < 0.05$). Their mean HR at rest significantly decreased during the training period ($p < 0.05$). The BP at rest did not change significantly. Subsequent to training, vital capacity was unchanged. However, forced expiratory volume in 1 second significantly increased ($p < 0.05$).

Comparisons of the maximal and submaximal exercise test variables before and after training (Table I) showed significant differences ($p < 0.05$). Maximal HR, systolic BP, HR-BP product and physical work capacity were significantly increased after training. Submaximal exercise average HR-BP and average ratings of perceived exertion were significantly lower after training. Within the elderly group there was a nonsignificant negative correlation between age and improved physical work capacity ($r = -0.11$).

The results of exercise tests before and after training in AMI and CABG patients are listed in Table II. The differences before and after training were significant in both AMI and CABG patients ($p < 0.05$). However, the changes were not significant between AMI and CABG patients even though CABG patients had a greater percent increase (48 vs 59%) in physical work capacity than AMI patients.

Table III lists the results of exercise testing before and after training in the elderly patients when subgrouped for use of β-blocking medications. There were significant differences before and after training in both groups ($p < 0.05$). Both groups had greater physical work capacities, lower submaximal average HR-BP product, and lower submaximal average ratings of perceived exertion after training. A comparison of the 2 groups for

TABLE III Test Results Before and After Training in Elderly Patients

	Before Training	After Training
β blockade (n = 25)		
Physical work capacity (METs)	5.1 ± 1.5	7.8 ± 1.4*
Average HR × BP × 10^{-2} (submaximal)	155 ± 38	125 ±28*
Average RPE (submaximal)	13 ± 2	11 ± 2*
No β blockade (n = 51)		
Physical work capacity (METs)	5.4 ± 1.2	8.2 ± 1.6*
Average HR × BP × 10^{-2} (submaximal)	182 ± 44†	149 ± 35*,†
Average RPE (submaximal)	12 ± 2	10 ± 2*

* $p < 0.05$.
† Significantly different ($p < 0.05$) from β-blockade group.
Abbreviations as in Table I.

differences in magnitudes of change revealed no significant difference, although the group without β-blocking therapy had a slightly greater increase in physical work capacity than the group with β-blocking therapy.

There was no significant difference between the elderly group and any other group with respect to the percentage of patients who received β-blocking medication ($p < 0.05$) (group I—23%, group II—25%, group III—38%, and group IV—33%). Therefore, these patients were included for the between-group comparisons. Table IV lists the results of exercise testing before and after training in each of the 4 age groups. All 4 groups evidenced significantly different pre- and posttraining variables ($p < 0.05$). After training, physical work capacity was greater, and submaximal average HR-BP product and ratings of perceived exertion were lower in all 4 groups. With the exception of physical work capacity in the youngest (group I) versus that in the elderly (group IV) patients, there were no significant differences in magnitudes of change between groups, although the elderly patient group had a significantly lower absolute physical work capacity at testing after training than the other 3 groups ($p < 0.05$).

Discussion

The aging process has been demonstrated to alter cardiorespiratory function with resultant diminished functional capacity.[21–23] In healthy, elderly subjects, improvement in endurance and functional capacity can be achieved with exercise training.[24,25] The present study suggests that this finding is also true in elderly persons with ischemic heart disease and that the improvement is similar to that manifested by younger patients. After training, our elderly cardiac patients demonstrated a significant increase in maximal exercise tolerance, a decrease in myocardial work (HR-BP product) at submaximal workloads, and a decrease in perception of effort at standardized work intensities. Higher maximal HR-BP product values after training suggest that the increased exercise capacity of our elderly patients was due to their ability to perform at higher myocardial oxygen demand levels.[26,27]

In 46 male cardiac patients (aged 37 to 68 years [mean age 54]) who had no exercise training, Savin et al[28] found a 25% increased peak oxygen uptake and a 10% decrease in submaximal HR-BP product during the initial weeks after recovery from AMI. Hence, it is possible that some of the improvement we noted after training was a result of "spontaneous improvement" unrelated to exercise training. However, in this study, in patients of similar age (40 to 64 years [mean 53]), there was an increase in physical work capacity of 48% and a decrease in submaximal HR-BP product of 17%. Elderly patients showed a 53% increase in physical work capacity and an 18% decrease in submaximal average HR-BP product. Although Savin et al[28] used direct measurement of oxygen uptake and this study used estimated oxygen uptake, the magnitudes of change in our patients were considerably greater than those reported by Savin, suggesting that the improvements were more than what would be expected from "spontaneous improvement" alone.

Cardiac patients have reported increases in self-confidence and less fear of physical exertion after training both with and without improvements in peripheral or cardiac measurements.[29–31] Thus, although the observed improvements shown in this study may represent training effects derived from peripheral and cardiac function adaptations, they may also have resulted, at least in part, from the patients' willingness to push themselves harder toward maximal physical work capacities after the program. The elderly patient group did show a significant increase in maximal HR from exercise tests before and after training (126 to 138 beats/min). Thus, the evaluation of standardized submaximal parameters as described previously is an important tool to measure training effects in these patients. However, no significant differences were seen in

TABLE IV Exercise Test Results Before and After Training in All Four Age Groups

	Before Training	After Training
Group I (mean age 40 ± 4 yrs)		
Physical work capacity (METs)	6.3 ± 1.6	9.8 ± 1.6*,†
Average HR × BP × 10^{-2} (submaximal)	170 ± 33	143 ± 33*
Average RPE (submaximal)	12 ± 2	9 ± 2*,†
Group II (mean age 50 ± 3 yrs)		
Physical work capacity (METs)	6.3 ± 1.3†	9.2 ± 1.4*,†
Average HR × BP × 10^{-2} (submaximal)	168 ± 46	134 ± 32*
Average RPE (submaximal)	12 ± 2	10 ± 2*
Group III (mean age 59 ± 3 yrs)		
Physical work capacity (METs)	6.0 ± 1.7	9.0 ± 1.7*,†
Average HR × BP × 10^{-2} (submaximal)	156 ± 40	135 ± 37*
Average RPE (submaximal)	12 ± 2	10 ± 2*
Group IV (mean age 70 ± 3 yrs)		
Physical work capacity (METs)	5.3 ± 1.3	8.1 ± 1.5*
Average HR × BP × 10^{-2} (submaximal)	173 ± 44	141 ± 35*
Average RPE (submaximal)	12 ± 2	10 ± 2*

* Significantly different from before training value ($p < 0.05$).
† Absolute value is significantly different from similar value in group IV ($p < 0.05$), although magnitudes of change are not significantly different with the exception of METs in group I vs METs in group IV.
Abbreviations as in Table I.

maximal ratings of perceived exertion between tests before and after training.

It is concluded that elderly male, cardiac patients benefit from participation in early exercise programs through enhanced functional capacity and improved psychologic responses to exertion. Furthermore, as a result of decreased submaximal myocardial oxygen demand, they may be less symptomatic during their daily routines, which should enhance the quality of their lives. Finally, elderly patients appear to be at no greater risk from participation in exercise programs than younger patients and should not be excluded from early exercise rehabilitation exercise programs simply on the basis of age.

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Early Positive Exercise Test and Extensive Coronary Disease: Effect of Antianginal Therapy

JHULAN MUKHARJI, MD, MARK KREMERS, MD, KIRK LIPSCOMB, MD, and C. GUNNAR BLOMQVIST, MD

The effect of antianginal therapy on the incidence of an early positive exercise response as a screening tool for 3-vessel and left main (LM) coronary artery disease (CAD) was examined. Fifty-seven men with stable angina pectoris underwent bicycle ergometry before and after long-acting nitrate or calcium antagonist therapy was instituted. An early positive response was defined as signs of myocardial ischemia at low levels of myocardial and total body workload (corresponding to a workload of less than 300 kpm/min). Thirty-nine patients (68%) had an early positive response before therapy, compared with 14 (24%) after therapy. Of 24 patients undergoing coronary angiography, 12 had 3-vessel CAD (including 2 with LM), 5 had 2-vessel CAD, 6 had 1-vessel CAD and 1 patient had no CAD. The sensitivity and specificity of an early positive response in predicting 3-vessel/LM CAD changed from 92% and 58% before to 42% and 75% after therapy. The positive and negative predictive values changed from 69% and 88% before to 63% and 63% after therapy. It is concluded that antianginal therapy reduces the value of an exercise test as a screening tool for 3-vessel/LM CAD.

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Exercise testing is often used as a prognostic tool in patients with known coronary artery disease (CAD). Early positive tests, defined as signs of myocardial ischemia at low levels of myocardial and total body workload, are associated with an increased likelihood of 3-vessel or left main (LM) CAD and a poor prognosis.[1–4] Because surgery may improve prognosis in subsets of these patients,[5] an early positive exercise test is frequently used to select patients for cardiac catheterization. The effect of antianginal drug therapy on the occurrence and accuracy of an early positive exercise test is not known. Therefore, the present study was performed to assess the incidence and implications of an early positive response in patients who underwent serial exercise testing before and after antianginal therapy, and to assess the effect of antianginal therapy on the ability of an early positive response to predict coronary artery anatomy.

From the Department of Internal Medicine (Cardiology Division), University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas. This study was supported in part by Ischemic SCOR Grant HL17669 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received July 9, 1984; revised manuscript received September 24, 1984, accepted September 25, 1984.

Address for reprints: Jhulan Mukharji, MD, Division of Cardiovascular Diseases, Medical College of Virginia, P.O. Box 36, Richmond, Virginia 23298.

Methods

The study group consisted of 61 men, aged 57 ± 7 years (mean ± standard deviation), who participated in study protocols that evaluated calcium antagonists (bepridil and lidoflazine) and a long-acting nitrate (Nitro-Bid®). Entry criteria for the study included typical stable angina pectoris with more than 5 episodes of chest pain per week for more than 6 months preceding enrollment. In addition, an ischemic ST-segment response (more than 1 mm of ST-segment depression) during previous exercise testing was required. All antianginal drugs except sublingual nitroglycerin were discontinued for more than 4 weeks before obtaining a baseline exercise study. Multistage upright bicycle exercise was performed on a Monark bicycle ergometer beginning at a workload of 150 kpm/min with increments of 150 kpm/3 min. Orthogonal Frank leads X, Y and Z were monitored continuously throughout the exercise test. Permanent electrocardiographic recordings at 25 mm/s were obtained in the final minute of each stage of exercise. Blood pressure (BP) was measured at rest, at the end of each stage, at exercise termination, and every 3 minutes for 6 minutes after termination. End points of the exercise test in this study included downsloping or horizontal ST depression more than 1 mm from the baseline, measured 80 ms after the J point in any lead, or incapacitating symptoms, including angina, dyspnea, weakness and fatigue. No patient was taking digitalis glycosides and no patient had other signs or symptoms that would constitute a reason to terminate the test.

An early positive test response was defined as the occurrence of significant ST deviation within the first 6 minutes of

TABLE I Comparison Between Total Study Group and Coronary Arteriography Group

	Total Study Group (%)	Coronary Arteriography Group (%)
No. of pts	57	24
Age	57 ± 7	56 ± 8
Risk factors	1.4	1.3
Baseline early +	39 (68) *	16 (66) †
After therapy early +	14 (25) *	8 (33) †

* $p < 0.01$; † $p < 0.05$.
Risk = diabetes mellitus, hypertension, smoking, prior myocardial infarction; + = positive response.

exercise (stage 2, corresponding to a workload of less than 300 kpm) or the failure to complete stage 2 and achieve at least 75% of age-predicted maximal heart rate (HR) in the absence of significant ST deviation.[1,2] After the baseline study, antianginal treatment was begun with long-acting nitrates (19 patients) and calcium antagonists (38 patients). The dosage of drugs was as follows: bepridil, 200 to 400 mg once daily (to tolerance); lidoflazine, 120 mg 3 times daily; and nitrobid, 6.5 mg twice daily. Exercise testing was subsequently repeated at a mean interval of 4 ± 3 months while patients continued to receive antianginal therapy. Coronary angiography was performed in 24 patients. Significant stenosis was defined as more than 50% luminal narrowing and the extent of disease was classified as 0-, 1-, 2- and 3-vessel, or LM CAD. Decisions regarding cardiac catheterization were made at the discretion of physicians involved in the management of individual patients.

Statistical analysis: Values are expressed as mean ± standard deviation. McNemar's test was used to assess the change in status (yes or no for an early positive response) from baseline to after therapy in the entire group and separately in the group that underwent angiography. A Student *t* test for paired observations was used to compare the change from before to after therapy in HR, HR-BP product, BP and exercise workload in each of 4 groups—early and before therapy, nonearly and before therapy, early and after therapy, and nonearly and after therapy.

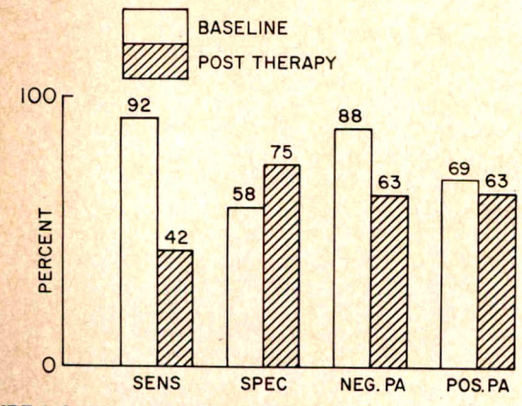

FIGURE 1. Sensitivity (SENS), specificity (SPEC) and predictive accuracy (PA) of an early positive exercise response for the detection of 3-vessel and left main coronary artery disease. Comparison between exercise tests performed before and after antianginal therapy in patients undergoing coronary arteriography. Numerical values indicate percentages. NEG. = negative; POS. = positive.

Analysis of variance with 1 repeated measure (before and after therapy) and 1 independent (or grouping) factor was used to compare the effect of therapy for BP, HR, HR-BP product and exercise workload in subjects who did vs those who did not undergo catheterization.

Results

In 1 patient unstable angina developed, and coronary artery bypass surgery was performed. Three patients were lost to follow-up before the second exercise test. Hence, complete data are available in 57 patients who had satisfied entry criteria for the study, including electrocardiographic evidence of myocardial ischemia during a previous exercise test. At the baseline exercise study, 39 patients (68%) had an early positive test response (Table I). Of these, 37 patients had 1 mm or more of ST-segment depression and 2 were unable to achieve more than 75% of maximal predicted HR and had a total exercise duration of less than 6 minutes (corresponding to a total body workload of less than 300 kpm). After initiation of antianginal therapy, only 14 patients (25%) had an early positive response ($p < 0.01$), all of whom had 1 mm or more of ST-segment depression in less than 6 minutes. Thirteen of these 14 patients had early positive responses at baseline as well. Baseline clinical characteristics were comparable within patient groups (Table II). No statistical differences were noted in baseline peak HR, peak systolic BP and HR-BP product when data were analyzed in patients grouped according to early positive responses before and after antianginal therapy (Table III). The overall peak workload achieved increased from a mean value of 302 ± 130 to 408 ± 123 kpm with therapy ($p < 0.001$). Similar significant increases were also noted individually in both patient groups (Table III). Antianginal drug treatment caused a 63% reduction in the occurrence of early positive tests. Finally, changes in total body work were compared among patients given various antianginal agents, and no significant differences were noted.

In the subgroup of 24 patients who underwent coronary arteriography, 16 (66%) early positive tests were noted at baseline (Table I). Eight patients (33%) continued to have an early positive test during antianginal therapy ($p < 0.05$). Twelve of the 24 patients (50%) had 3-vessel CAD, 5 (21%) had 2-vessel CAD, 6 (25%) had 1-vessel CAD, and in 1 patient there was no significant CAD by angiography. Two patients had LM CAD in addition to 3-vessel CAD. Before therapy an early positive test had a sensitivity of 92% (11 of 12) and a specificity of 58% (7 of 12) in detecting LM or 3-vessel CAD (Fig. 1). Both patients with LM CAD were correctly identified. After therapy, the sensitivity decreased to 42% (5 of 12) and the specificity increased to 75% (9 of 12) (Fig. 1). The predictive accuracy of a positive test for LM or 3-vessel CAD before therapy was 69% (11 of 16) and of a negative test 88% (7 of 8). After treatment these values changed to 63% and 63%, respectively (Fig. 1). Patients who converted from an early positive to a non-early positive test with antianginal therapy included 6 with 3-vessel CAD, including 1 patient with LM CAD. Baseline characteristics and re-

TABLE II Clinical Characteristics of Patient Group*

	Baseline		After Therapy	
	Early + n (%)	Non-Early + n (%)	Early + n (%)	Non-Early + n (%)
No. of pts	39 (68)	18 (32)	14 (25)	43 (75)
Age (±SD)	58 ± 6	55 ± 7	58 ± 6	57 ± 7
Diabetes	8 (21)	1 (6)	2 (14)	7 (16)
Hypertension	20 (51)	5 (28)	8 (57)	17 (40)
Cigarette smoking	9 (23)	8 (44)	3 (21)	14 (33)
Previous MI	20 (51)	11 (61)	9 (64)	22 (51)

* Patients are grouped according to early and non-early positive exercise response, before and after antianginal therapy.
MI = myocardial infarction; SD = standard deviation; + = positive response.

sponse to therapy were comparable in the overall study group and in the group that underwent coronary arteriography (Table I). No significant differences were found between patients with 3-vessel/LM CAD and 0- to 2-vessel CAD in left ventricular ejection fraction, left ventricular end-diastolic pressure, left ventricular mass and incidence of wall motion abnormality.

Discussion

This study addresses the issue of using the exercise test as a screening tool to identify patients with severe CAD, and examines the effect of antianginal therapy on the use of an early positive ischemic response for this purpose. Although an ideal screening test should be highly sensitive and specific, it may be considered adequate if it is highly sensitive and possesses a reasonable degree of specificity and predictive value. Our data suggest that in patients with a high probability of CAD, an early positive exercise test response before the institution of antianginal therapy is a highly sensitive marker of extensive disease; however, antianginal therapy substantially reduces the sensitivity of the early positive response without markedly improving its specificity (Fig. 1).

Several exercise criteria have been used as markers of 3-vessel and LM CAD. These include limited total work capacity, abnormal BP and HR response, severity and duration of ST-segment depression, and early onset of ischemic ST-segment changes.[1–4,6–10] Exercise-induced hypotension in patients without valve dysfunction is a specific but insensitive marker for extensive disease.[6] None of our patients had such a response. Ellestad and Wan[2] and Schneider et al[4] showed that ST-segment change at a reduced workload is a better predictor of severe CAD than the extent of ST depression. Additionally, in our institution[11] and in others, exercise is terminated after the development of more than 1 mm of unequivocal ST-segment deviation from baseline. Greater ST-segment change is therefore infrequently seen. McNeer et al[1] and Ellestad and Wan[2] determined that an abnormal chronotropic response in the absence of β-blocking therapy is significantly associated with severe CAD. Consequently, we used ST-segment depression at a reduced workload and an attenuated chronotropic response with limited total work capacity as markers of extensive CAD.

TABLE III Exercise Response Before and After Therapy: Comparison Between Patient Groups*

		Baseline	
		Early Positive (n = 39)	Non-Early Positive (n = 18)
Peak BP	B	179 ± 25 } NS	176 ± 20 } NS
	T	176 ± 25 }	180 ± 17 }
Peak HR	B	128 ± 13 } NS	128 ± 15 } NS
	T	127 ± 14 }	130 ± 20 }
RPP × 10^3	B	230 ± 42 } NS	232 ± 55 } NS
	T	223 ± 39 }	237 ± 52 }
Workload (Kpm)	B	240 ± 102 } †	437 ± 70 } †
	T	359 ± 103 }	513 ± 95 }

* Patients are grouped according to early and non-early positive exercise response, before and after antianginal therapy.
† $p < 0.001$.
All values are expressed as mean ± standard deviation.
B = baseline; BP = blood pressure; HR = heart rate; kpm = kilopond-meters per minute; NS = not significant; RPP = rate-pressure product; T = during therapy.

To our knowledge, no previously published study has assessed the effect of antianginal therapy on the prognostic implications of an early positive exercise test. McNeer et al[1] found no change in the order of importance of prognostic variables when propranolol was considered. Blomqvist et al[12] found that β-blocking drugs did not obscure differences in mean peak workloads among patients grouped according to coronary anatomy. These studies considered differences in mean values among groups and did not report changes in individual responses using patients as their own controls. Nixon et al[13] reported that although propranolol did not affect the frequency of an ischemic response to exercise in groups of patients with LM or 3-vessel CAD, it did abolish differences in peak workload that might be used to distinguish the extent and severity of CAD. Our study supports and extends these findings.

This study has certain limitations, and the results must be interpreted accordingly. First, we examined a select group of men with typical angina pectoris and a high probability of CAD. Extending the results to other patient groups could therefore be misleading. Second, anatomic correlations were available in 24 of the 57 patients and the possibility of selection bias must be considered. However, the exercise variables, response

TABLE IV Patients With and Without Coronary Arteriography: Comparison of Exercise Response

		No Coronary Arteriography		Coronary Arteriography	
No. of pts		33		24	
Peak HR	B	130	NS	126	
	T	127	NS	129	
Peak BP	B	180	NS	175	
	T	178	NS	176	
RPP	B	235	NS	223	
	T	226	NS	230	
Workload (kpm)	B	307	NS	296	
	T	422	* NS	388	*

* $p < 0.001$.
Abbreviations as in Table III.

to therapy and baseline characteristics were similar in the overall study group and in the group undergoing coronary arteriography (Tables I and IV); the distribution of the extent of CAD is similar to findings reported in patients with stable angina pectoris.[14] Therefore, we believe that significant selection bias is not a major concern. Finally, despite its popular usage, the somewhat simplistic 3-vessel classification of coronary anatomy does not completely define prognosis. Hence, our findings cannot be extrapolated to define prognosis completely, which is influenced as well by several other variables. The clinical significance of changes in prognostic exercise variables induced by antianginal therapy is currently unknown. Further studies using large patient populations followed over a long period are required to determine this relation. One may reasonably conclude that conversion from the early positive to the non-early positive response group by antianginal therapy is not an assurance of favorable coronary anatomy, and that exercise testing should ideally be performed without antianginal therapy when screening for severe CAD.

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Improved Accuracy of the Exercise Electrocardiogram: Identification of Three-Vessel Coronary Disease in Stable Angina Pectoris by Analysis of Peak Rate-Related Changes in ST Segments

PETER M. OKIN, MD, PAUL KLIGFIELD, MD, OLIVIER AMEISEN, MD, HARVEY L. GOLDBERG, MD, and JEFFREY S. BORER, MD

Exercise electrocardiography has relatively poor specificity and predictive accuracy for 3-vessel coronary artery disease (CAD) when conventional diagnostic criteria are used. However, electrocardiographic evaluation using linear regression analysis of the heart-rate (HR)-related change in ST-segment depression (ST/HR slope) is reported to accurately distinguish patients with from those without CAD, and to accurately separate patients with 1-, 2- and 3-vessel CAD. To assess the applicability of this method and to compare it with conventional interpretation, retrospective evaluation of 50 patients in whom exercise electrocardiography and coronary cineangiography had been performed for suspected CAD was conducted using a modified ST/HR slope analysis limited to leads V_5, V_6 and aVF. Eighteen patients had 3-vessel, 22 had 2-vessel, 6 had 1-vessel and 4 had no CAD. Standard electrocardiographic criteria (1 mm or more of horizontal or downsloping ST depression) identified 3-vessel CAD with a sensitivity of 78%, specificity of 56% and positive predictive value of only 50%. Peak ST/HR slope criteria ($\geq$6.0 μV/beat/min) identified 3-vessel CAD with a sensitivity of 78%, specificity of 97% and positive predictive value of 93%. The overall test accuracy using measured peak ST/HR slope was 90%, compared with 64% for standard ST-depression criteria. In conclusion, analysis of the peak ST/HR slope can greatly improve the diagnostic accuracy of exercise electrocardiography, and further prospective study of this method is indicated.

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The clinical evaluation of coronary artery disease (CAD) often involves interpretation of the exercise electrocardiogram. However, the accurate identification of patients with and without CAD is limited by poor test sensitivity and specificity,[1–5] and assessment of the severity of CAD among patients with angina pectoris is limited by availability of predictive discriminators.[1–3,5–8] The need for accurate noninvasive identification of 3-vessel and left main CAD is highlighted by studies that demonstrate improved survival with coronary artery bypass surgery in these disease subsets.[9–11]

Evaluation of the exercise electrocardiogram using linear regression analysis of the peak heart rate (HR)–related change in ST-segment depression with exercise has recently been reported to accurately separate patients with no, 1-, 2- and 3-vessel CAD.[12–14] To assess the applicability of this method for the identification of 3-vessel and left main CAD, we evaluated 50 patients in whom exercise electrocardiography and coronary cineangiography were performed for suspected coronary ischemia.

From the Division of Cardiology, Department of Medicine, New York Hospital-Cornell Medical Center, New York, New York. Manuscript received July 3, 1984; revised manuscript received September 17, 1984, accepted September 18, 1984.

Address for reprints: Paul Kligfield, MD, New York Hospital-Cornell Medical Center, 525 East 68th Street, New York, New York 10021.

Methods

Patients: Records of 50 consecutive patients with stable angina pectoris who had undergone both exercise electrocardiography and coronary angiography were reviewed. Patients with coexisting valvular heart disease, myocardial infarction within 6 weeks of exercise testing and left bundle branch block were excluded from analysis.

Coronary angiography: Selective coronary cineangiography was performed with multiple views in all patients. The extent of CAD was determined as the percent narrowing of the luminal diameter based on views in multiple planes. Patients

TABLE I Comparison of Patient Characteristics According to Extent of Coronary Artery Disease

Patient Characteristics	0-, 1- and 2-Vessel CAD (n = 32)	3-Vessel CAD (n = 18)	p Value
Age (yr)	50 ± 1.7	57 ± 2.8	<0.05
Duration of ex (stages)	2.6 ± 0.2	1.9 ± 0.2	<0.05
Magnitude of ST depression (mm)	0.9 ± 0.2	2.0 ± 0.3	<0.001
Peak HR (beats/min)	132 ± 5	121 ± 6	NS
Change in HR (beats/min)	60 ± 5	50 ± 4	NS
Peak systolic BP (mm Hg)	152 ± 6	137 ± 7	NS
Change in systolic BP (mm Hg)	31 ± 5	23 ± 5	NS
Peak DP (mm Hg·beats/min)	19,882 ± 1,329	16,949 ± 1,568	NS
Change in DP (mm Hg·beats/min)	11,468 ± 1,060	8,796 ± 1,222	NS

Mean values presented with the standard error of the mean as index of dispersion.
BP = blood pressure; CAD = coronary artery disease; DP = double product; ex = exercise; HR = heart rate; NS = not significant.

were considered to have significant CAD if any of the major coronary arteries had luminal narrowing of 75% or greater. Three-vessel CAD was defined as simultaneous obstruction in proximal portions of the left anterior descending artery, right coronary artery and left circumflex coronary artery or its first large marginal branch.[12] Isolated left main CAD would have been scored as equivalent to 2-vessel CAD, but in this series it occurred only in patients with additional 3-vessel CAD.

Exercise electrocardiography: Exercise electrocardiography was performed on a treadmill using standard or modified Bruce protocols. Although target HRs were sought, clinical studies were terminated when indicated because of anginal chest pain, a reduction in systolic blood pressure of 10 mm Hg or more, the development of 3 consecutive ventricular premature complexes or limiting fatigue, dyspnea or light-headedness. Twelve-lead electrocardiograms were recorded after each minute of exercise. The baseline HR and baseline amount of ST-segment depression were determined from the upright electrocardiogram at rest, recorded before exercise.

The magnitude of ST-segment depression (in microvolts) to the nearest 25 μV was determined by measuring the ST-segment displacement below the end of the PR segment at a point 70 ms after the J point, using a ruler calibrated to 0.25 mm. Six to 8 electrocardiographic complexes were measured in each lead. Standard amplitude calibration (1 mm = 100 μV) was used.

The HR-related change in ST-segment depression (ST/HR slope in μV/beat/min) was calculated according to a previously reported technique[12–14] from measured ST-segment depression and HR separately for leads aVF, V_5 and V_6. Each electrocardiographic lead produced exercise data points that related ST-segment depression as a dependent variable to heart rate as an independent variable. The slope derived from linear regression analysis of the final 3 points was compared with slopes obtained by including progressively earlier points.[12–14] For each patient, the highest calculated ST/HR slope with a statistically significant correlation coefficient (maximal ST/HR slope) from among the 3 leads analyzed was selected as the test result.

In addition, exercise tests were evaluated using standard electrocardiographic criteria[1]: A type 1 response was defined as 1 mm or more of downsloping (type 1a) or horizontal (type 1b) ST-segment depression, a type 2 response as 1 mm or greater of upsloping ST-segment depression, and a negative test as less than 1 mm of ST-segment depression.[1] Patients with a type 1 response were also evaluated for the presence of stage 1 onset of ST-segment depression, ST-segment depression persisting longer than 8 minutes, and for the presence of ST-segment depression of at least 2 mm.

Definitions of test performance: The *sensitivity* of a test criterion for recognition of 3-vessel CAD was defined as the percentage of patients with 3-vessel CAD who had a positive test result according to that test criterion. The *specificity* of a test criterion for 3-vessel CAD was defined as the percentage of patients without 3-vessel CAD who had a negative test result according to that test criterion. *Overall test accuracy* was defined as the percentage of patients correctly diagnosed as either having or not having 3-vessel CAD; this was the proportion of combined true-positive and true-negative test results based on each test criterion. The *positive predictive value* of a test criterion for 3-vessel CAD was defined as the percentage of patients with a positive test result who had 3-vessel CAD.

Data analysis: Electrocardiographic criteria were compared in terms of test sensitivity, specificity, positive predictive value and overall test accuracy. Because predictive value and test accuracy depend on population prevalence of disease,[5,15,16] observed sensitivity and specificity data were used to calculate positive predictive value and overall test accuracy over a wide range of 3-vessel CAD prevalence to assess test applicability in varying populations. To compare group mean values between subsets of patients, the Student *t* test for unpaired samples was used.

Results

Distribution of disease and subgroup characteristics: The group comprised 42 men and 8 women whose mean age was 53 years (range 31 to 74). Eighteen patients had 3-vessel CAD, including 5 with additional left main CAD; 22 had 2-vessel, 6 had 1-vessel and 4 had no significant CAD. At the time of exercise testing, 56% of the patients (10 of 18 with 3-vessel and 18 of 32 with less than 3-vessel CAD) were taking β-adrenergic blocking drugs, and 22 (44%) had a history of myocardial infarction.

The exercise performance of the 18 patients with 3-vessel CAD and the 32 patients with no, 1- or 2-vessel CAD are compared in Table I. Patients with 3-vessel CAD were older, had a greater amount of ST-segment depression at end exercise, and exercised for a significantly shorter period. However, patients with and without 3-vessel CAD were similar with respect to peak HR achieved, exercise HR response, systolic blood pressure response and double product achieved during

TABLE II Recognition of Three-Vessel Coronary Artery Disease by Exercise Electrocardiographic Criteria

Test Criteria	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Overall Test Accuracy (%)	Negative Predictive Value (%)
Type 1a response	33	78	46	62	68
Type 1b response	44	78	53	66	71
Type 1 response	78	56	50	64	82
and stage 1 onset	56	72	53	66	74
and duration ≥8 min	44	75	50	64	71
and ST depression ≥2 mm	61	75	58	70	77
Type 1 and 2 responses	100	38	47	60	100
ST/HR slope ≥6.0 (μV/beat/min)	78	97	93	90	89

ST/HR slope = maximal ST segment/heart rate slope (see text).

exercise, although trends toward lower performance can be seen in patients with 3-vessel CAD.

ST-segment/heart rate relation: The exercise ST/HR slope calculated for each patient is shown relative to the extent of CAD in Figure 1. The maximal ST/HR slope was 1.3 ± 0.3 μV/beat/min (range 0.8 to 2.2) in patients with no significant CAD, 2.2 ± 0.5 (range 1.2 to 4.2) in patients with 1-vessel CAD, 3.5 ± 0.4 (range 0.7 to 7.4) in patients with 2-vessel CAD and 9.1 ± 1.2 (range 2.8 to 20.0) in patients with 3-vessel CAD. All differences were statistically significant ($p < 0.001$ to $p < 0.05$) except for comparison of patients with 1-vessel and those with no CAD. The maximal ST/HR slope in the 5 patients with combined 3-vessel and additional left main CAD was 10.8 ± 1.3 (range 8.2 to 15.7). This is not statistically different from the maximal ST/HR slope in the 13 patients with 3-vessel CAD alone (8.5 ± 1.5 [range 2.8 to 20.0]).

The ability of the maximal ST/HR slope to correctly distinguish patients with 3-vessel CAD from among a similarly symptomatic group with less extensive CAD is shown in Table II. Using a maximal ST/HR slope of ≥6.0 μV/beat/min as a test criterion for the recognition of 3-vessel CAD has a sensitivity of 78%, specificity of 97%, positive predictive value of 93% and an overall test accuracy of 90%.

Standard electrocardiographic criteria: Standard evaluation of the exercise electrocardiograms revealed a type 1 response in 28 patients (56%), a type 2 response in 10 patients (20%) and a negative response in 12 patients (24%). The type 1 responses were further subclassified into type 1a (13 patients) and type 1b (15 patients).

The ability of standard electrocardiographic criteria to distinguish patients with 3-vessel CAD from other patients is also shown in Table II. A type 1 response as a test criterion for the identification of 3-vessel CAD has a sensitivity of 78%, specificity of 56% and a positive predictive value of only 50%. The addition of either stage 1 onset of ST-segment depression, prolonged duration of ST-segment depression, or ST-segment depression of 2 mm or greater to a type 1 response increases test specificity at the expense of lower sensitivity, without significantly improving the positive predictive value. The inclusion of type 2 in addition to type 1 responses as a positive test criterion improves the sensitivity for detecting 3-vessel CAD in this group to 100%, but decreases specificity to 38%. The overall test accuracy using standard electrocardiographic analysis, including combinations of criteria, ranges from 60 to 70%.

Effect of beta-blocking drugs: The effects of β-blocking drugs on exercise performance, electrocardiographic findings and the ST/HR slope are listed in Table III. Among patients with 1-, 2- and 3-vessel CAD, the mean ST/HR slope is the same in subgroups with the same extent of CAD, regardless of the presence or

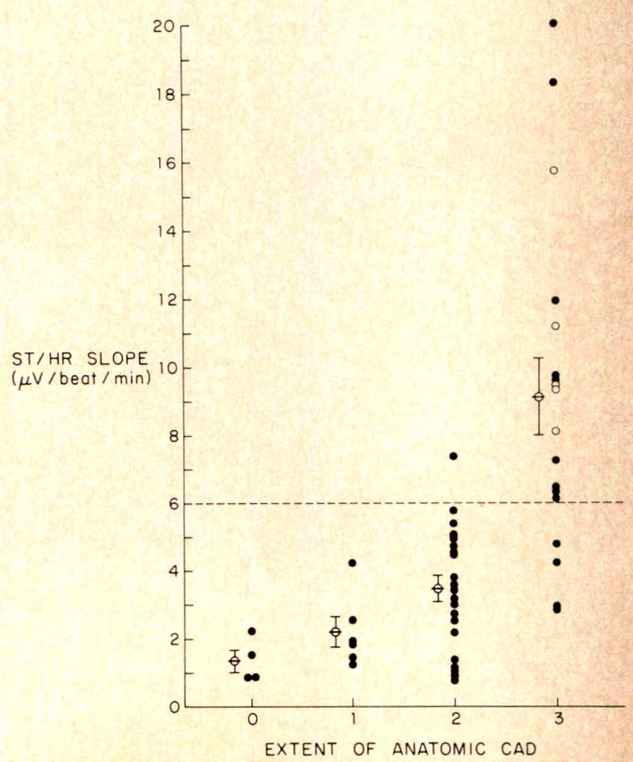

FIGURE 1. Relation of maximal ST-segment/heart rate (ST/HR) slope to the extent of coronary artery disease (CAD). A slope of 6.0 μV/beat/min (**broken line**) separates patients with 3-vessel disease from others with overall test accuracy of 90%. Patients with additional left main disease are represented by **open circles.**

TABLE III Comparison of Exercise Test Findings in Patients With and Without Beta-Adrenergic Blocking Drugs, According to Extent of Coronary Artery Disease

Exercise Findings	0-, 1- and 2-Vessel CAD		3-Vessel CAD	
	With β Blocker	Without β Blocker	With β Blocker	Without β Blocker
ST/HR slope (μV/beat/min)	2.9 ± 0.4	3.1 ± 0.5	8.8 ± 1.9	9.5 ± 1.2
Duration of ex (stages)	2.6 ± 0.3	2.6 ± 0.4	1.9 ± 0.3	2.1 ± 0.3
Magnitude of ST depression (mm)	0.8 ± 0.2	1.0 ± 0.2	1.4 ± 0.2	2.8 ± 0.4*
Peak HR (beats/min)	128 ± 6	138 ± 8	109 ± 7	136 ± 7*
Change in HR (beats/min)	55 ± 5	66 ± 8	44 ± 5	58 ± 7
Peak SBP (mm Hg)	146 ± 8	158 ± 8	119 ± 6	160 ± 11*
Change in SBP (mm Hg)	27 ± 7	34 ± 7	13 ± 2	36 ± 8*
Peak DP (mm Hg·beats/min)	18,958 ± 1,529	21,855 ± 1,893	13,136 ± 1,333	21,716 ± 2,175†
Change in DP (mm Hg·beats/min)	10,215 ± 1,228	14,505 ± 1,553*	6,091 ± 859	12,177 ± 2,009*

All values are expressed as mean ± standard error of the mean.
* $p < 0.05$; † $p < 0.001$.
CAD = coronary artery disease; DP = double product; ex = exercise; HR = heart rate; SBP = systolic blood pressure; ST/HR slope = maximal ST segment/heart rate slope (see text).

absence of β blockade. Constancy of the ST/HR slope was found in therapeutic subgroups of patients with 3-vessel CAD despite the significantly greater magnitude of ST depression, higher HRs, and higher blood pressures achieved by patients not taking β-blocking drugs. A similar relation is seen in the patients with less than 3-vessel CAD, and for the change in HR with exercise in both groups, but these differences do not achieve statistical significance. All patients with less than 3-vessel CAD are grouped for clarity in Table III, although findings apply to individual subgroups as well.

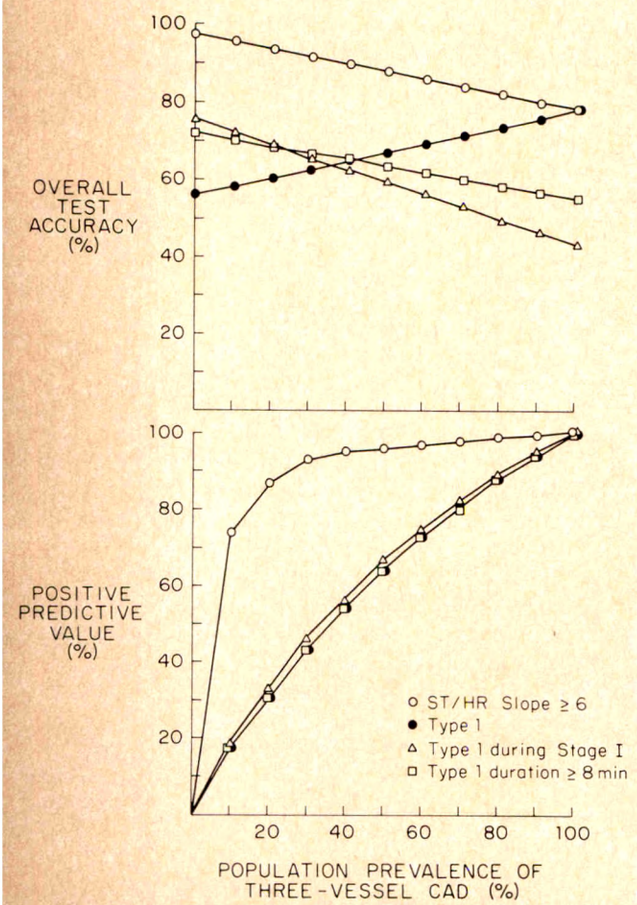

FIGURE 2. Effect of population prevalence on overall test accuracy and positive predictive value of various test parameters for the identification of 3-vessel coronary artery disease (CAD). Greater test accuracy and predictive value of the ST-segment/heart rate (ST/HR) slope are apparent at any disease prevalence. The method is strong in the prevalence range, where 3-vessel disease is found in most clinical populations.

Bayesian analysis: Figure 2 shows the positive predictive value and overall test accuracy for the maximal ST/HR slope, type 1 response, stage 1 onset of ST-segment depression and prolonged duration of ST-segment depression as a calculated function of the prevalence of 3-vessel CAD in the group. The maximal ST/HR slope has the greatest positive predictive value and overall test accuracy for any assumed population.

Discussion

Our data confirm the ability of a rate-normalized measure of exercise-induced ST-segment depression, the ST/HR slope, to identify patients with 3-vessel disease within a CAD population. In contrast is the significantly lower overall test accuracy of standard electrocardiographic criteria for the detection of extensive disease. These findings support the theoretical basis of ST-segment analysis developed by Elamin et al,[12,13] who demonstrated the ability of the ST/HR slope to accurately assess the presence or absence of CAD and to precisely quantify the severity of CAD according to 1-, 2-, and 3-vessel involvement with no overlap between groups.

Rationale for ST/HR slope analysis: The ST/HR slope is an index of functional myocardial ischemia.[12–14] Excellent correlation has been shown between myocardial oxygen consumption and HR in normal subjects, in patients with CAD and in experimental animals.[17–19] From these data, it is apparent that myocardial ischemia should be provoked with smaller increases in HR in patients with more extensive CAD. In addition, ST-segment depression with exercise can be related to the extent of myocardial ischemia caused by underlying CAD,[20–22] even though ST-segment depression alone is not a highly sensitive predictor of CAD in any given patient.[23,24] These observations suggest that ST-seg-

ment depression associated with a smaller increase in HR during exercise should reflect more severe myocardial oxygen supply-demand imbalance than the same magnitude of ST depression occurring with a greater HR response. In effect, the ST/HR slope method normalizes ST-segment depression for the extent of augmentation of myocardial oxygen demand occurring during exercise, and this normalization appears independent of the duration of effort.

Effect of beta-blocking drugs: In patients who were taking β-blocking drugs, no difference in mean ST/HR slopes was found compared with patients with a similar extent of CAD who were not taking these drugs. This finding is in agreement with that Kardash et al,[14] who found no difference in ST/HR slope in 21 patients tested both with and without β-blocking therapy.

Beta-blocking drugs can reduce the magnitude of exercise-related ST-segment depression[25,26] and also decrease the HR response to exercise.[25–27] Because the slopes of lines relating myocardial oxygen consumption to HR during exercise in subjects given β-blocking drugs do not significantly differ from those not receiving drugs,[27] it might be predicted that the observed ST/HR slope in patients treated with β-blocking therapy would remain constant despite clinical improvement with medication. Our data suggest that a parallel decrease in ST-segment depression and HR response to exercise is reponsible for the observed independence of the ST/HR slope from β blockade.

Standard electrocardiographic criteria: Limitations of the standard exercise electrocardiogram[1–8,15,16] are highlighted by our findings. Although horizontal or downsloping ST-segment depression (type 1 response) identified 3-vessel CAD with a sensitivity of 78%, specificity was only 56% and the positive predictive value only 50%. Therefore, this standard electrocardiographic criterion is of limited accuracy in populations with a nonpredominance of 3-vessel CAD. Tightening electrocardiographic criteria for a positive test to include only type 1 responses occurring during stage 1, or those associated with prolonged ST-segment depression or with 2 mm or greater ST-segment depression, improved test specificity, but only at the cost of significant decreases in test sensitivity. Conversely, broadening the criteria for a positive test to include upsloping ST depression (type 2 response) increased test sensitivity at the cost of specificity.

Bayesian analysis: Assuming constant test sensitivity and specificity, the predictive value and overall test accuracy of any test criterion can be mathematically calculated for any postulated prevalence of disease.[5,15,16] This allows for the prediction of test applicability in varying hypothetic populations. Comparison of the calculated overall test accuracy and positive predictive value of the ST/HR slope, type 1 response, stage 1 onset of ST-segment depression and prolonged type 1 ST-segment depression for the identification of 3-vessel CAD in populations with varying prevalence of 3-vessel CAD suggests the diagnostic advantage of the maximal ST/HR slope. This advantage of the ST/HR slope method in calculated test accuracy and positive predictive value is greatest over the CAD prevalence range of 10 to 50%, which is the prevalence range most commonly found in clinical populations undergoing evaluation for known or suspected CAD.[28,29] Thus, incorporation of ST/HR slope analysis into exercise electrocardiographic criteria for recognition of 3-vessel CAD should improve true-positive diagnoses without markedly increasing false-positive diagnoses in patients with CAD.

Limitations of study design: Findings favorable to the ST/HR slope analysis emerge despite intrinsic study design bias against the method. Because our study was retrospective, there were fewer than optimal numbers of data points available for each patient. The available HR increments for each patient were large, reducing test precision. Furthermore, we evaluated only 3 leads, with less precise measurement of ST-segment change compared with previous analyses.[12–14] Nevertheless, even with these limitations, improved accuracy of the exercise electrocardiogram is clear.

An additional limitation bearing on general applicability of the ST/HR slope method involves patient selection in our study. Although consecutive patients who met entry criteria form the basis of this report, we cannot assume that the group studied is representative, because all patients by definition underwent angiography. Catheterization in this group might have been based on potentially predictive symptoms, and in some cases may have been prompted by the electrocardiographic findings at exercise testing. Although in no case was the ST/HR slope a pretest consideration, prospective validation is required to exclude possible bias introduced by otherwise unrecognized electrocardiographic changes.

Implications: The ability of the ST/HR slope to identify the extent of CAD has several important implications. First, noninvasive identification of patients with 3-vessel CAD may be possible with a high degree of sensitivity and specificity, even in the presence of β-blocking drugs. Second, the method may provide the ability to evaluate progression of CAD in an individual patient by following serial ST/HR slopes. Third, patients may be followed up after coronary artery bypass surgery or coronary angioplasty for occult graft closure or reocclusion by comparing an immediate postprocedure ST/HR slope with subsequent tests. Finally, the ST/HR slope analysis may provide more accurate understanding of "false-positive" electrocardiographic responses to exercise associated with abnormal loading conditions and with drugs, if, as expected, the ST-segment–heart rate relation is different in these populations than in patients with CAD.

The number of possible uses for the ST/HR slope highlight the importance of further prospective validation of the technique. However, the present slope analysis is cumbersome for routine application, making a rapid and more standardized method of analysis an important goal. This may be accomplished by computerized measurement of ST-segment displacement combined with computerized linear regression analysis.

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Effect of Coffee on Exercise-Induced Angina Pectoris Due to Coronary Artery Disease in Habitual Coffee Drinkers

KENNETH M. PITERS, MD, ANTONIO COLOMBO, MD, HAROLD G. OLSON, MD, and SAMUEL M. BUTMAN, MD

The acute effects of coffee on exercise-induced angina were studied in 17 men with coronary artery disease using a double-blind treadmill protocol. Ingestion of either 1 or 2 cups of caffeinated coffee increased the exercise duration until onset of angina (8 and 12%, respectively, $p < 0.05$), whereas decaffeinated coffee had no effect. The extent of ST-segment depression and the heart rate-blood pressure product at angina were similar after drinking caffeinated and decaffeinated coffee. Exercise duration until 0.1 mV of ST-segment depression, as well as the heart rate, blood pressure and double product at angina and at 0.1 mV of ST-segment depression were similar after drinking caffeinated or decaffeinated coffee. The mean serum caffeine levels (± standard deviation) after ingestion of 1 and 2 cups of caffeinated coffee were 1.97 ± 1.0 and 3.89 ± 1.6 μg/ml, respectively. The acute ingestion of 1 to 2 cups of caffeinated coffee had no deleterious effect on exercise-induced angina pectoris in patients with coronary artery disease. (Am J Cardiol 1985;55:277–280)

It has been estimated that 82% of persons older than age 18 years in the United States consume an average of 186 mg/day of caffeine in coffee, tea, cola beverages and over-the-counter prescriptions.[1] Although a limited amount of data on the arrhythmogenicity of caffeine is available,[2,3] its effect on exercise-induced angina pectoris is unknown. Accordingly, we designed a double-blind treadmill protocol to assess the acute effects of caffeinated and decaffeinated coffee on exercise-induced angina pectoris in patients with chronic stable angina due to coronary artery disease (CAD).

Methods

Seventeen male subjects with chronic stable angina and an abnormal exercise test limited by angina with 0.1 mV or greater horizontal or downsloping ST depression were selected. The patients ranged in age from 40 to 74 years (mean ± standard deviation 59 ± 9). Ten patients were in New York Heart Association class II, and 7 were in class III. All 17 patients had CAD proved by angiography with 75% luminal narrowing in at least 1 major artery. Two patients had 1-vessel CAD, 7 had 2-vessel CAD and 8 had 3-vessel CAD; none had left main CAD. The left ventricular ejection fraction was 65 ± 11% (mean ± standard deviation) (range 41 to 83%). All patients consumed at least 1 cup of coffee daily. Daily coffee consumption averaged 3.7 cups per patient (range 1 to 7).

Patients were excluded if they had myocardial infarction within 3 months, unstable angina, chronic left or right bundle branch block, symptomatic congestive heart failure, complex ventricular arrhythmias (Lown class III or higher) seen on the electrocardiogram before exercise, or valvular heart disease. Also excluded were patients who took quinidine, procainamide or digitalis. Patients with hiatal hernia, esophagitis, peptic ulcer disease or gallbladder disease were also excluded.

Patients were studied on 3 consecutive days in the fasting state without receiving their morning antianginal therapy. Seven of the 17 patients were taking chronic oral propranolol (80 to 200 mg/day in divided doses; mean 114 mg/day). One patient was taking nifedipine 30 mg/day. The other 9 patients were taking nitrates alone. Patients served as their own control subjects over the 3-day study period. No patient smoked cigarettes, coffee or tea for 12 hours before exercise.

Patients underwent paired Bruce protocol treadmill tests each day, totaling 6 tests over 3 days. The first treadmill test served as a control. After 1 hour of rest, 2 cups of hot black coffee were consumed over 20 minutes. On any given day this consisted randomly of either 2 cups of caffeinated coffee, 2 cups of decaffeinated coffee, or a combination of 1 cup of each. The combination of decaffeinated coffee with caffeinated coffee blinded the administration of 1 cup of caffeinated coffee to both patient and observer. Thirty minutes after coffee ingestion, blood was drawn for caffeine levels and a second treadmill test was performed. Patients were instructed to stop exercise when they experienced angina as they would with ordinary activity. Blood pressures were obtained every 90 seconds and with angina at end exercise.

From the Cardiology Section, Medical Service, Long Beach Veterans Administration Medical Center, and the University of California, Irvine.
Manuscript received July 30, 1984; revised manuscript received October 25, 1984, accepted October 26, 1984.
Address for reprints: Kenneth M. Piters, MD, Cardiology Section, Veterans Administration Medical Center, 5901 East Seventh Street, Long Beach, California 90822.

TABLE I Values at Rest Before and After Coffee Ingestion

Value*	Control	Decaffeinated Coffee	Control	1 Cup of Caffeinated Coffee	Control	2 Cups of Caffeinated Coffee
HR (beats/min)	81 ± 11	84 ± 12	80 ± 12	82 ± 13	83 ± 11	82 ± 13
SBP (mm Hg)	121 ± 15	120 ± 16	123 ± 15	118 ± 19	118 ± 16	122 ± 16
HR-SBP product (mm Hg/min)	9,775 ± 1,742	10,044 ± 1,594	9,846 ± 2,039	9,643 ± 2,400	9,877 ± 2,162	9,986 ± 1,752

* Values are expressed as mean ± 1 standard deviation.
HR = heart rate; SBP = systolic blood pressure.

TABLE II Exercise Values at the Onset of Angina Before and After Coffee Ingestion

Value*	Control	Decaffeinated Coffee	Control	1 Cup of Caffeinated Coffee	Coffee	2 Cups of Caffeinated Coffee
Exercise duration (sec)	394 ± 177	399 ± 165	399 ± 139	436 ± 163†	401 ± 158	454 ± 179†
HR (beats/min)	125 ± 15	123 ± 16	121 ± 13	126 ± 15	128 ± 15	131 ± 17
SBP (mm Hg)	157 ± 16	157 ± 14	160 ± 19	157 ± 18	156 ± 17	158 ± 15
HR-SBP product (mm Hg/min)	19,574 ± 3,327	19,343 ± 2,989	19,464 ± 3,493	19,776 ± 3,299	19,951 ± 3,422	20,739 ± 3,858
ST depression (mm)	1.6 ± 1.0	1.4 ± 0.9	1.6 ± 0.9	1.6 ± 1.0	1.5 ± 1.0	1.5 ± 0.9

* Values are expressed as mean ± 1 standard deviation. † $p < 0.05$ compared with control.
Abbreviations as in Table I.

Electrocardiographic leads aVF, V_1 and V_5 were monitored continuously during exercise. Exercise ST depression beyond baseline ST at rest was measured from electrocardiographic recordings in the lead with the most shift. ST depression was evaluated 80 ms past the J point on 3 consecutive QRS complexes.

Exercise duration until 0.1 mV of ST depression and exercise duration until onset of angina were measured from electrocardiographic recordings. Heart rate-blood pressure product was calculated at the time of 0.1 mV ST depression and at angina at end exercise.

Two cardiologists performed the exercise tests in an identical manner in the same air-conditioned room. Each patient was supervised by the same cardiologist over the 3-day period.

Coffee was prepared by mixing 8 ounces of heated water with 1 heaping teaspoon of instant coffee (Taster's Choice® caffeinated and decaffeinated brands), with no milk or sugar.

Caffeine levels were assayed by Smith, Kline and French Laboratories using high pressure liquid chromatography, accurate to 0.5 μg/ml.[4]

Repeated measures analysis of variance was used to compare all 6 treatments (consisting of 3 control treadmill tests before and 3 study treadmill tests after the 3 coffee combinations). Both rest and exercise data were examined. In cases of significant F values, Scheffe's test was used to ascertain which pairs of means were significantly different. This allowed comparison of the 3 treatments of decaffeinated coffee, 1 and 2 cups of caffeinated coffee. In addition, patients who took propranolol were compared with those who did not by a split-plot analysis of variance with least squares analysis design. Statistical significance was defined as $p < 0.05$. Data are presented as mean ±1 standard deviation.

Results

There was no significant change in baseline mean heart rate at rest, systolic blood pressure at rest or heart rate-blood pressure product at rest after the ingestion of any of the 3 coffee combinations (Table I).

There was no significant difference in mean exercise duration until the development of angina after 2 cups of decaffeinated coffee compared with results in the control treadmill tests. However, 1 and 2 cups of caffeinated coffee resulted in significant prolongation of exercise over controls (mean increase of 37 seconds for 1 cup and 53 seconds for 2 cups of caffeinated coffee, $p < 0.05$) (Table II).

There was no significant difference in the mean heart rate, systolic blood pressure and heart rate-blood pressure product at angina on treadmill tests after any of the 3 coffee combinations. There was a trend toward an increase in heart rate-blood pressure product at angina after 2 cups of caffeinated coffee which did not reach statistical significance (Table II).

There was no significant difference in the extent of ST depression at angina after any of the 3 coffee combinations.

There was no significant difference in exercise duration until onset of 0.1 mV of ST depression after any of the 3 coffee combinations (Table III). Although there was a trend toward an increased exercise duration until 0.1 mV of ST depression after 2 cups of caffeinated coffee, this did not reach statistical significance. In addition, there was no significant change in heart rate, systolic blood pressure or heart rate-blood pressure product at 0.1 mV of ST depression after any of the 3 coffee combinations (Table III).

The 7 patients who received long-term therapy with propranolol were analyzed separately and compared with the 10 patients who did not receive propranolol. Rest and peak exercise heart rate and blood pressure before and after coffee ingestion were similar in both groups. In addition, there was no statistically significant difference between the 2 groups in exercise time to 0.1 mV ST depression or to angina after any of the 3 coffee combinations.

TABLE III Exercise Values at 0.1 mV of ST Depression Before and After Coffee Ingestion

Value*	Control	Decaffeinated Coffee	Control	1 Cup of Caffeinated Coffee	Control	2 Cups of Caffeinated Coffee
Exercise duration (sec)	298 ± 157	307 ± 153	312 ± 132	313 ± 144	290 ± 136	319 ± 132
HR (beats/min)	115 ± 15	114 ± 17	112 ± 16	111 ± 15	115 ± 15	115 ± 16
SBP (mm Hg)	151 ± 17	149 ± 16	153 ± 18	149 ± 18	148 ± 18	150 ± 16
HR-SBP product (mm Hg/min)	17,388 ± 3,394	16,964 ± 3,253	17,191 ± 3,878	16,613 ± 3,310	17,184 ± 3,723	17,316 ± 3,488

* Values are expressed as mean ± standard deviation.
Abbreviations as in Table I.

TABLE IV Prevalence and Frequency of Rest and Exercise Premature Atrial Contractions and Premature Ventricular Contractions

	Control	Decaffeinated Coffee	Control	1 Cup of Caffeinated Coffee	Control	2 Cups of Caffeinated Coffee
Premature Atrial Contractions						
No. of pts with ≥1 PAC on rest ECG	0	0	3	1	1	1
No. of PACs on rest ECG (all 17 pts)	0	0	12	1	1	1
No. of pts with ≥1 PAC with exercise	3	3	5	4	3	2
No. of PACs with exercise (all 17 pts)	18	9	17	14	8	3
Premature Ventricular Contractions						
No. of pts with ≥1 PVC on rest ECG	0	1	2	0	0	1
No. of PVCs on rest ECG (all 17 pts)	0	4	2	0	0	1
No. of pts with ≥1 PVC with exercise	3	4	3	5	7	5
No. of PVCs with exercise (all 17 pts)	11	12	24	45	20	17

ECG = electrocardiogram; PAC = premature atrial contraction; PVC = premature ventricular contraction.

There was no significant increase in the prevalence of resting or exercise-induced premature atrial or ventricular contractions after any of the coffee combinations (Table IV). One patient with unifocal premature ventricular contractions on a control treadmill test experienced an increased number but not complexity of premature ventricular contractions during exercise after 1 and 2 cups of caffeinated coffee.

The mean serum caffeine level 30 minutes after 2 cups of decaffeinated coffee was 0.73 ± 0.3 μg/ml. The serum caffeine level after 1 cup of caffeinated coffee was 1.97 ± 1.0 μg/ml and after 2 cups of caffeinated coffee was 3.89 ± 1.6 μg/ml. The mean serum caffeine level after 2 cups of caffeinated coffee was significantly higher than after 1 cup of caffeinated coffee and both were significantly higher than after 2 cups of decaffeinated coffee ($p < 0.01$).

Discussion

The principal pharmacologic agent in coffee is generally accepted to be caffeine—a methylated xanthine. One cup of coffee contains about 85 mg of caffeine. The per capita intake of caffeine in the United States has been estimated to be 200 mg/day,[1] equivalent to 2 cups of caffeinated coffee.

We evaluated the effects of coffee on exercise in 17 men with chronic stable angina and proved CAD, who were habitual coffee drinkers (mean, 3.7 cups/day). Two cups of caffeinated coffee had no deleterious effects on exercise-induced angina, ST depression, premature ventricular contractions or exercise duration. Exercise duration until angina was significantly prolonged after both 1 and 2 cups of caffeinated coffee (mean increase, 37 seconds after 1 cup and 53 seconds after 2 cups of caffeinated coffee). This increase in the exercise time to development of angina after coffee ingestion was accompanied by a statistically insignificant trend toward a higher heart rate-blood pressure product (an index of myocardial O_2 demand), with no change in the extent of ST depression at angina compared with results in the control treadmill tests.

The mechanisms for this increase in exercise time to angina after caffeinated coffee are speculative but could include central nervous system stimulant and analgesic properties,[5] shift in substrate use from carbohydrate to free fatty acids,[6] increase in myocardial O_2 supply, decrease in myocardial O_2 demand, or any combination of these factors.

Explanation of the increase in exercise duration purely by central nervous system stimulation and delay

in perception of angina would seem unlikely, because one would expect more profound ischemia at angina, whereas similar degrees of ST depression were manifested after caffeinated and decaffeinated coffee. However, central nervous system stimulation may be partially responsible for the increased exercise time after caffeinated coffee.

Previous studies support the contention that caffeine acutely increases the work of the heart in normal subjects,[7,8] although the caffeine effect on cardiac work during exercise is unknown in patients with CAD. The trend toward increased cardiac work at the onset of angina (at similar degrees of ischemia) after caffeinated coffee occurred with increased exercise times. This implies a beneficial shift in the O_2 supply-demand ratio. Diuretic properties of caffeine[9] may mimic a nitrate effect by decreasing preload and therefore wall tension and myocardial O_2 consumption at a given double product. Alternatively, coronary flow may have improved.

The effect of the methylxanthines on coronary blood flow, especially in humans, remains controversial. The belief that they might increase coronary blood flow has led to their use in patients with angina.[10] Animal studies of the effects of xanthines on coronary flow are conflicting,[11,12] whereas human studies are lacking. In this study, exercise duration before 0.1 mV of ST depression was prolonged after 2 cups of caffeinated coffee, but because this prolongation was not significant, no definite conclusion regarding coronary flow can be reached.

The possibility that training effect accounted for the increased exercise time to angina after caffeinated coffee is unlikely, because there was no such increase after decaffeinated coffee compared with results of the control treadmill tests. Moreover, there could be no cumulative training effect over the 3-day study period because the coffee combinations were given randomly, resulting in an equal distribution of the coffee combinations between the first and third days of the study.

Resting hemodynamic variables were unaffected by caffeine in the patients in this study. This is consistent with the hemodynamic study of Gould et al,[7] although data on normal volunteers suggest that an increase in blood pressure should accompany the ingestion of 2 cups of caffeinated coffee.[13] Blood levels of caffeine, similar to other studies after 2 cups of caffeinated coffee,[2] indicate adequate absorption of the drug in our patients. Because the 10 patients who did not receive propranolol had similar rest and exercise heart rates and blood pressures before and after coffee ingestion (similar to those who did take propranolol), it is unlikely that the residual effects of propranolol 12 hours after the last dose account for the blunted hemodynamic response seen in the entire group. Patients with CAD may behave differently than normal subjects after coffee ingestion. Alternatively, the lack of effect of coffee on hemodynamics at rest in our study may be explained by tolerance to the effects of caffeine with chronic coffee use. Tolerance to caffeine has been described and can result in a blunted hemodynamic response within 1 to 4 days of initiation.[14] All patients in our study drank coffee chronically. Perhaps exercise duration in our patients would have decreased had the heart rate-blood pressure products at rest increased with coffee ingestion.

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Comparative hemodynamic profiles...[1]

INOCOR VS. DOBUTAMINE, DOPAMINE

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↓	↓	Systemic vascular resistance
↑[2]	↔	Myocardial oxygen demand
↑	↓ ↔	Mean arterial pressure
↑	↔	Heart rate
↔[3]	↑[4]	Renal blood flow
YES	NO	Tachyphylaxis

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4. Data on file, Winthrop-Breon Laboratories.

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

Winthrop-Breon

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31249

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardi inotropic agents with vasodilator activity, distinct from digitalis glycosides catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-te management of congestive heart failure in patients who can be closely monitored a who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of conge tive heart failure. Because of limited experience and potential for serious adver effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who c be closely monitored and who have not responded adequately to digitalis, diureti and/or vasodilators. Although most patients have been studied hemodynamically periods only up to 24 hours, some patients were studied for longer periods a demonstrated consistent hemodynamic and clinical effects. The duration of thera should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients w are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfit

PRECAUTIONS *General*: INOCOR lactate injection should not be used in patients w severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstructi Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrop subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure a heart rate should be monitored and the rate of infusion slowed or stopped in patie showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insuffici cardiac filling pressure to respond adequately to INOCOR lactate injection, in whi case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the ve high-risk population treated. While amrinone per se has not been shown to arrhythmogenic, the potential for arrhythmia, present in congestive heart failure its may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERS REACTIONS).

LABORATORY TESTS *Fluid and electrolytes*: Fluid and electrolyte changes and ren function should be carefully monitored during amrinone lactate therapy. Improveme in cardiac output with resultant diuresis may necessitate a reduction in the dose diuretic. Potassium loss due to excessive diuresis may predispose digitalized patie to arrhythmias. Therefore, hypokalemia should be corrected by potassium supp mentation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical ma festations have been observed in patients in whom INOCOR lactate injection was us concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, me prolol, propranolol; hydralazine, prazosin; isosorbide dinitrate, nitroglycerine; chlorth done, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captop heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was us concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpac disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C*: In New Zealand white rabbits, amrinor has been shown to reduce fetal skeletal and gross external malformations at oral dos of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabb using oral doses up to 32 mg/kg/day did not confirm this finding. No malformatio were seen in rats receiving amrinone intravenously at the maximum dose use 15 mg/kg/day (approximately the recommended daily IV dose for patients with co gestive heart failure). There are no adequate and well-controlled studies in pregna women. Amrinone should be used during pregnancy only if the potential bene justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone administered to nursing women, since it is not known whether it is excreted in hum milk.

ADVERSE REACTIONS *Thrombocytopenia*: Intravenous INOCOR lactate injecti resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCO lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdomir pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCO lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/da amrinone showed dose-related hepatotoxicity manifested either as enzyme elevatic or hepatic cell necrosis or both. Hepatotoxicity has been observed in man followir long-term oral dosing and has been observed, in a limited experience (0.2%), followir IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity rea tions in patients treated with oral amrinone for about two weeks. Signs and symptom were variable but included pericarditis, pleuritis, and ascites (one case); myositis wi interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); ar vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). Th first patient died, not necessarily of the possible reaction, while the last two resolve with discontinuation of therapy. None of the cases were rechallenged, so attribution amrinone is not certain, but possible hypersensitivity reactions should be considered any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinic studies include fever (0.9%), chest pain (0.2%), and burning at the site of injectic (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotensic because of its vasodilator effect. If this occurs, amrinone administration should b reduced or discontinued. No specific antidote is known, but general measures f circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions*: Asympt matic platelet count reduction (to less than 150,000/mm³) may be reversed within or week of a decrease in drug dosage. Further, with no change in drug dosage, the cou may stabilize at lower than predrug levels without any clinical sequelae. Predrug platel counts and frequent platelet counts during therapy are recommended to assist decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm³ occur, the following actions may b considered:

- Maintain total daily dose unchanged, since in some cases counts have eith stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds th potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequent with IV therapy, should severe or debilitating ones occur, the physician may wish t reduce dosage or discontinue the drug based on the usual benefit-to-ris considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity ha rarely been observed. If acute marked alterations in liver enzymes occur together wit clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinon therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms, thes nonspecific changes should be evaluated on an individual basis. The clinician ma wish to continue amrinone and reduce the dosage or discontinue the drug based o the usual benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOCO 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactat equivalent to 5 mg base and 0.25 mg sodium metabisulfite in water for injection.

Propranolol-Verapamil Versus Propranolol-Nifedipine in Severe Angina Pectoris of Effort: A Randomized, Double-Blind, Crossover Study

MICHAEL D. WINNIFORD, MD, KAY L. FULTON, RN, JAMES R. CORBETT, MD, CHARLES H. CROFT, MD, and L. DAVID HILLIS, MD

To compare a propranolol-verapamil with a propranolol-nifedipine combination in patients with severe angina of effort, 16 patients (11 men and 5 women, aged 56 ± 8 years [mean ± standard deviation]) with more than 5 episodes/week of angina and a positive exercise tolerance test despite propranolol (229 ± 44 mg/day [range 180 to 360]) were maintained on this dose of propranolol and, in addition, received verapamil (360 mg/day) and nifedipine (60 mg/day) for 3 weeks each in a double-blind, randomized fashion. In comparison with propranolol alone, anginal frequency and nitroglycerin usage were reduced by propranolol-verapamil but not by propranolol-nifedipine. Exercise time (standard Bruce protocol) was similar for the 2 combinations (6.4 ± 2.0 minutes with propranolol-verapamil, 6.6 ± 2.1 minutes with propranolol-nifedipine, difference not significant), but the magnitude of ST-segment depression at peak exercise was less ($p < 0.05$) during propranolol-verapamil (0.03 ± 0.06 mV) than during propranolol alone (0.18 ± 0.07 mV) and propranolol-nifedipine (0.08 ± 0.07 mV). Left ventricular ejection fraction at rest was higher ($p < 0.05$) with propranolol-nifedipine (0.62 ± 0.10) than with propranolol-verapamil (0.58 ± 0.10), but neither differed from ejection fraction at rest with propranolol alone (0.59 ± 0.08). Ejection fraction at peak exercise was similar during all 3 periods. In 2 patients, verapamil caused weakness, lightheadedness, and severe sinus bradycardia (40 to 48 beats/min), and the dosage was reduced (blindly) to 240 mg/day, with the alleviation of bradycardia and associated symptoms. Thus, in patients with severe angina of effort with propranolol alone, the addition of verapamil is more effective than the addition of nifedipine in reducing anginal frequency, nitroglycerin usage, and the magnitude of the electrocardiographic response to exercise. Although both combinations are generally safe and well-tolerated, in an occasional patient symptomatic sinus bradycardia develops during therapy with propranolol-verapamil; therefore, this combination must be given carefully.

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Over the past 15 years, the β-adrenergic blocking agents, such as propranolol, have been effective in patients with stable angina of effort.[1–5] Later, the calcium antagonists, including verapamil[6–9] and nifedipine,[10,11] have proved efficacious in this patient population. However, some patients have limiting angina despite maximally tolerated doses of propranolol or 1 of the calcium antagonists, and in these patients, a combination of propranolol and a calcium antagonist may be especially beneficial. In fact, previous studies have demonstrated that a propranolol-verapamil combination[12–14] and a propranolol-nifedipine combination[15] are better than either agent alone in patients whose angina is particularly severe. The present randomized, double-blind and crossover study was performed to compare a propranolol-verapamil combination and a propranolol-nifedipine combination in patients with severe angina of effort.

From the Departments of Internal Medicine (Cardiovascular Division) and Radiology (Nuclear Medicine), the University of Texas Health Science Center, Dallas, Texas. This work was supported in part by Ischemic SCOR grant HL-17669 from the National Institutes of Health, Bethesda, Maryland. Manuscript received August 16, 1984; revised manuscript received November 1, 1984, accepted November 2, 1984.

Address for reprints: Michael D. Winniford, MD, Room L5.134, University of Texas Health Science Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

Methods

Study patients: Sixteen patients (11 men and 5 women, aged 56 ± 8 years [mean ± standard deviation]) with limiting angina of effort despite therapy with propranolol (range 180 to 360 mg/day [average 229 ± 44]), were enrolled in the study. Each had more than 5 episodes of typical angina per week and a positive exercise tolerance test (with chest pain and greater

than 0.1 mV ST-segment depression) during propranolol therapy. Selective coronary arteriography was performed in 13 patients, all of whom had significant coronary artery disease (defined as greater than 70% narrowing of luminal diameter) (3-vessel disease in 7, 2-vessel disease in 5 and 1-vessel in 1). The other 3 patients had typical angina as well as historical and electrocardiographic evidence of previous myocardial infarction. One patient had undergone coronary artery bypass surgery in the remote past.

Of the 16 patients, 2 were maintained throughout the study on a stable dose of slow-release transdermal nitroglycerin (10 mg/day). In these patients, several attempts to taper or discontinue nitrates caused a worsening of angina. All patients were instructed to use sublingual nitroglycerin only for relief of anginal episodes. No other cardiac medications were given during the study.

Patients with any of the following were excluded from the study: congestive heart failure, as reflected by cardiomegaly and pulmonary vascular redistribution on chest x-ray; uncontrolled systemic arterial hypertension (diastolic arterial pressure greater than 115 mm Hg); hypotension (systolic arterial pressure less than 90 mm Hg); associated valvular or congenital cardiac disease; renal disease (serum creatinine more than 2.5 mg%); hepatic disease (serum bilirubin more than 2.5 mg%); any terminal illness; certain electrocardiographic abnormalities, including bundle branch block, severe bradycardia (heart rate less than 50 beats/min with propranolol), second- or third-degree atrioventricular block, or atrial flutter or fibrillation; or concomitant therapy with disopyramide or an investigational agent.

Study design: Each patient who entered the study received a maximally tolerated dose of propranolol, which was continued throughout the study. After informed consent was obtained, each received single-blind placebo for 2 weeks, after which he or she was randomly assigned to 1 of 2 groups for the remaining 7 weeks of the study: two 3-week periods of verapamil (360 mg/day in 3 equal doses) and nifedipine (60 mg/day in 3 equal doses), administered in random order and separated by a 1-week period of single-blind placebo. During the 2 periods of combination propranolol-calcium antagonist therapy, neither the physicians nor the patients knew which calcium antagonist was being given.

Variables assessed: *Clinical response to therapy:* Each patient was seen weekly by 1 of us, and the following were quantitated: (1) episodes of angina per week (recorded daily by the patient in a diary), (2) nitroglycerin tablets used per week (assessed by tablet count), and (3) adverse effects (recorded by the patient in a diary).

Exercise tolerance testing: Upright treadmill exercise: At the end of each treatment period, each patient had treadmill exercise testing according to a standard Bruce protocol 1½ to 2 hours after the regularly scheduled morning dose of propranolol and study medication. Exercise was continued until the occurrence of exhaustion, angina of at least moderate severity, frequent ventricular ectopy, or a markedly positive electrocardiographic response. The following variables were measured: (1) heart rate at rest and peak exercise, (2) heart rate-systolic arterial pressure double product at rest and peak exercise, (3) total exercise duration (in minutes), and (4) maximal ST-segment depression (in millivolts) from the isoelectric point.

Supine bicycle exercise with radionuclide ventriculography: After 2 weeks of each treatment, each patient had maximal supine bicycle exercise testing with simultaneous equilibrium-gated blood pool scintigraphy. As with treadmill exercise testing, these studies were performed 1½ to 2 hours after a regularly scheduled morning dose of propranolol and study medication. Exercise was begun at 200 kpm/min and increased incrementally by 200 kpm every 4 minutes until exhaustion, angina of at least moderate severity, or frequent ventricular ectopy. From each of these studies, the scintigraphic response to exercise was assessed, as reflected by left ventricular ejection fraction at rest and peak exercise, as previously described.[8,16,17]

Ambulatory electrocardiographic monitoring: At the end of the second week of each treatment period, ambulatory electrocardiographic (Holter) monitoring was performed for 24 hours, and the tapes were analyzed for PR interval, atrioventricular conduction disturbances and average heart rates.

Serum propranolol and verapamil concentrations: At the end of each treatment period (immediately before treadmill exercise testing), blood was obtained from each patient for the measurement of serum propranolol and verapamil concentrations.

Statistical analyses: All patient diaries, nitroglycerin tablet counts, Holter monitor recordings and exercise tolerance tests (treadmill and supine bicycle) were analyzed without knowledge of the order in which verapamil and nifedipine were given. The clinical characteristics of the patients initially assigned to verapamil were compared with those in the patients initially assigned to nifedipine; there were no differences, confirming that the initial assignment was random. For each variable, a repeated measures analysis of variance was performed to determine if some groups were different from others, after which the Newman-Keuls multiple comparisons procedure was performed. An unpaired t test was used to compare treatment responders and nonresponders. In comparing rest and peak exercise values during treatment with the same pharmacologic agent, the paired t test was used. For all analyses, a p value <0.05 was considered significant.[18,19]

Results

Patient compliance and tolerance of the medications: Patient compliance was excellent during all treatment periods (Table I). Of the 16 patients, 14 tolerated full doses of verapamil and nifedipine without difficulty. In the other 2 (both of whom had a resting heart rate less than 55 beats/min with propranolol alone), full-dose (360 mg/day) verapamil caused weakness, lightheadedness, and a sinus bradycardia of 40 to 48 beats/min with intermittent junctional escape beats. In these, the verapamil dosage was (blindly) reduced to 240 mg/day (120 mg twice daily), with the resultant alleviation of bradycardia and its associated symptoms.

The serum propranolol concentrations were similar during the 3 treatment periods and averaged 196 ± 133 ng/ml (range 32 to 438). The serum verapamil concentrations averaged 313 ± 143 ng/ml (range 130 to 609).

Responses to combination therapy: *Clinical responses to therapy:* Anginal frequency and nitroglycerin usage were similar during treatment with propranolol-verapamil and propranolol-nifedipine (Table I). However, in comparison to propranolol alone, anginal frequency and nitroglycerin usage were significantly reduced only during propranolol-verapamil. The 2 patients who received slow-release transdermal nitroglycerin during the study responded similarly to the 2 combinations (4.0 and 0.3 anginal episodes/week with propranolol-verapamil, 4.3 and 0.3 episodes/week with propranolol-nifedipine, respectively).

In comparison with propranolol alone, 7 patients responded to propranolol-verapamil with a more than 50% reduction in anginal frequency. During propranolol

TABLE I Clinical, Hemodynamic, Electrocardiographic and Scintigraphic Responses to Therapy

Variable	Propranolol	Propranolol-Verapamil	Propranolol-Nifedipine
Data Obtained from Patient Diaries			
Episodes of angina/wk	7.0 ± 5.9	3.6 ± 6.0*	5.1 ± 5.6
NTG tablets used/wk	5.0 ± 5.6	2.4 ± 5.7*	2.9 ± 4.8
Data Obtained from Treadmill Exercise Tolerance Testing			
HR (beats/min): rest	60 ± 7	58 ± 5	61 ± 7
HR (beats/min): peak ex	103 ± 12	91 ± 13*	99 ± 12†
SAP (mm Hg): rest	140 ± 23	126 ± 16*	124 ± 19*
SAP (mm Hg): peak ex	161 ± 29	146 ± 21*	146 ± 23*
HR-SAP double product ($\times 10^3$): rest	8.4 ± 1.6	7.3 ± 1.1*	7.6 ± 1.4*
HR-SAP double product ($\times 10^3$): peak ex	16.6 ± 3.7	13.3 ± 2.9*	14.5 ± 3.0*
Total ex time (min)	5.7 ± 1.9	6.4 ± 2.0	6.6 ± 2.1
Max ST-segment depression during ex (mV)	0.18 ± 0.07	0.03 ± 0.06*	0.08 ± 0.07*,†
Data Obtained From Supine Bicycle Exercise Testing with Radionuclide Ventriculography			
LVEF: rest	0.59 ± 0.08	0.58 ± 0.10	0.62 ± 0.10†
LVEF: peak ex	0.59 ± 0.14	0.59 ± 0.15	0.63 ± 0.15
Data Obtained from Ambulatory Electrocardiographic (Holter) Monitoring			
PR interval (ms)	170 ± 20	190 ± 30*	170 ± 20†
Average HR (beats/min)	68 ± 10	62 ± 6*	68 ± 7†
Miscellaneous			
Compliance	99%	100%	99%

All values are expressed as mean ± standard deviation.
* $p < 0.05$ compared with propranolol alone; † $p < 0.05$ compared with propranolol-verapamil.
ex = exercise; HR = heart rate; LVEF = left ventricular ejection fraction; NTG = nitroglycerin; SAP = systolic arterial pressure.

therapy alone, these 7 "responders" had a significantly higher average heart rate (73 ± 12 beats/min) than the 9 "nonresponders" (63 ± 5 beats/min, $p < 0.05$). In all other respects, the propranolol-verapamil responders and nonresponders were similar. In comparison with propranolol alone, 6 patients responded to propranolol-nifedipine with a more than 50% reduction in anginal frequency. There were no differences in clinical, hemodynamic, electrocardiographic or scintigraphic variables in the 6 propranolol-nifedipine responders and the remaining 10 nonresponders.

During propranolol therapy alone, 1 patient had shortness of breath. During treatment with propranolol-verapamil, 2 patients had constipation. During propranolol-nifedipine treatment, 1 patient complained of flushing, 1 had pedal edema and 1 noted constipation.

Responses to treadmill exercise tolerance testing: At rest and during peak exercise, the heart rate-systolic arterial pressure double products during propranolol-verapamil and propranolol-nifedipine were similar to one another and lower than during propranolol alone (Table I). Total exercise time was similar for the 2 combinations.

Four patients had electrocardiographic voltage criteria for left ventricular hypertrophy,[20] 2 of whom had evidence of left ventricular strain. Each had further ST-segment depression greater than 0.20 mV (average 0.24 ± 0.20 mV) and chest pain during exercise testing. In the 16 patients, the magnitude of ST-segment depression at peak exercise was less ($p < 0.05$) during propranolol-verapamil than during propranolol-nifedipine treatment (Table I). During propranolol-verapamil treatment, 5 patients had angina during exercise testing, and they averaged 0.10 ± 0.08 mV of ST-segment depression. The remaining 11 patients in whom angina did not occur with this combination during exercise testing averaged 0.01 ± 0.02 mV of ST-segment depression ($p = 0.004$). With propranolol-nifedipine, the 7 patients who had angina during exercise testing averaged 0.09 ± 0.07 mV of ST-segment depression, whereas the other 9 patients in whom angina did not occur during exercise testing had 0.07 ± 0.07 mV of ST-segment depression (difference not significant).

Scintigraphic responses to supine bicycle exercise: At rest, the ventricular ejection fraction was higher ($p < 0.05$) during propranolol-nifedipine than during propranolol-verapamil treatment (Table I). However, the ejection fraction at rest during therapy with the 2 combinations was not significantly different from propranolol alone (Table I). At peak exercise, the ejection fraction during the 3 treatment periods was not significantly different (Table I). During the study, no patient had symptoms or signs of left ventricular failure. In 1 patient, the left ventricular ejection fraction at rest decreased from 0.44 with propranolol alone to 0.31 with propranolol-verapamil and 0.32 with propranolol-nifedipine.

Ambulatory electrocardiographic responses to therapy: With propranolol-verapamil, 6 patients had asymptomatic prolongation of the PR interval (0.21 to 0.25 second), 2 of whom had a prolonged PR interval with propranolol-nifedipine. No patient had second- or third-degree heart block during the study. The average heart rate with propranolol-verapamil was lower than

with propranolol alone and propranolol-nifedipine (Table I).

Discussion

When given alone, propranolol,[1–5] verapamil[6–9] and nifedipine[10,11] are effective in patients with angina of effort, and the combined administration of propranolol and either verapamil or nifedipine is usually beneficial in patients whose angina is severe. Although previous studies have shown that both propranolol-verapamil[12–14] and propranolol-nifedipine[15] are better than either agent alone in this patient population, none has compared these drug combinations with one another. The present randomized and double-blind assessment shows that in some ways, propranolol-verapamil is better than propranolol-nifedipine in treating patients with severe angina of effort. Although propranolol-verapamil and propranolol-nifedipine were of similar overall clinical efficacy in these patients, only propranolol-verapamil reduced anginal frequency and nitroglycerin usage in comparison with propranolol alone (Table I). Furthermore, propranolol-verapamil reduced the magnitude of exercise-induced ST-segment depression to a greater extent than propranolol-nifedipine (Table I). This greater antiischemic effect was limited to those in whom angina did not occur during exercise testing with combination therapy.

Antianginal mechanisms of propranolol-verapamil and propranolol-nifedipine: *Propranolol* reduces myocardial oxygen demands by decreasing the major determinants of myocardial oxygen consumption (heart rate, left ventricular contractility and systemic arterial pressure).[21–23] In addition, it may inhibit platelet aggregation[24] and increase the delivery of oxygen to tissues (such as the myocardium) by altering the affinity of hemoglobin for oxygen.[25] Propranolol does not cause coronary vasodilatation, and in patients with coronary arterial spasm, it may even induce vasoconstriction.[26] Like propranolol, *verapamil* diminishes myocardial oxygen demands (by reducing heart rate, left ventricular contractility and systemic arterial pressure),[27,28] but it also causes coronary vasodilatation and, therefore, may augment anterograde and retrograde coronary blood flow.[29] *Nifedipine* reduces myocardial oxygen demands by lowering systemic arterial pressure (and, as a result, left ventricular wall tension); in the doses given clinically, it does not exert a negative chronotropic or inotropic effect.[30] Like verapamil, nifedipine causes coronary vasodilatation and may improve coronary blood flow.

Because the β-adrenergic blocking drugs and calcium antagonists, in some ways, have complementary antianginal mechanisms, their combined administration may be beneficial in patients with severe angina of effort. For example, the increase in heart rate that often occurs with nifedipine may be prevented or at least blunted by concomitant propranolol, with a resultant decrease in myocardial oxygen demands. Alternatively, the propensity of propranolol to increase coronary vascular resistance in patients in whom coronary arterial spasm is operative may be prevented by the direct vasodilating influence of verapamil or nifedipine. Previous studies[12–15] have shown that each of the 2 drug combinations is superior to either agent alone in patients with angina of effort.

In comparison to propranolol alone, the increase in heart rate-systolic arterial pressure double product (an estimate of myocardial oxygen demand) caused by exercise was reduced by the 2 combinations by somewhat different mechanisms. The addition of verapamil to propranolol induced a decrease in heart rate and systolic arterial pressure, whereas the addition of nifedipine produced a decrease only in the latter. The patients who responded favorably to the addition of verapamil had a higher average heart rate with propranolol alone than those who failed to respond.

Although total exercise duration was not significantly prolonged during either combination, the majority of patients who received combination therapy stopped exercise because of fatigue and did not experience angina. Thus, the failure to observe an increase in exercise duration during combination therapy may reflect a close angina-to-fatigue relation in these patients. Furthermore, the mechanism by which propranolol-verapamil seemed to exert a greater antiischemic effect in patients who discontinued exercise without angina is not clear, but a propranolol-verapamil combination could conceivably reduce myocardial oxygen demands more effectively than a propranolol-nifedipine combination.

Adverse effects of combination therapy: Because propranolol and verapamil exert negative inotropic and chronotropic effects, their combined use may cause left ventricular failure, marked bradycardia or atrioventricular block. None of the 16 patients had symptoms or signs of left ventricular failure during propranolol-verapamil therapy, and the addition of verapamil did not reduce resting or peak exercise left ventricular ejection fraction in comparison with propranolol alone (Table I). Two patients (in whom the heart rates at rest during propranolol therapy alone were 51 and 54 beats/min, respectively) had weakness and lightheadedness during this combination and were noted to have a sinus bradycardia of 40 to 48 beats/min with intermittent junctional escape beats. In both, the dose of study medication was reduced from 3 to 2 times daily (and, in both, the study medication was verapamil). This change in verapamil dosage (to 240 mg/day) caused an alleviation of symptoms, and the heart rate increased to 50 to 55 beats/min. Asymptomatic first-degree atrioventricular block was noted in 6 patients during propranolol-verapamil therapy and in 2 during propranolol-nifedipine therapy, but more advanced heart block did not occur during the study. Although the incidence of adverse effects was low, patients with congestive heart failure or known conduction system disease were excluded from enrollment. Clearly, both propranolol-verapamil and propranolol-nifedipine should be administered with caution, especially in patients with 1 of these abnormalities. A propranolol-verapamil combination is of special concern, however, because it may produce a marked negative inotropic or chronotropic effect.

Strengths and weaknesses of the study: The present study has several strengths. First, it is a randomized, double-blind and crossover comparison of propranolol-verapamil and propranolol-nifedipine.

Second, the patients accurately represented those in whom combination β-blocking–calcium antagonist therapy is most often considered—namely, patients with severe, limiting angina of effort in whom substantial doses of propranolol are not totally effective. At the same time, the study has certain limitations. Each patient received a fixed dose of verapamil (360 mg/day) and nifedipine (60 mg/day), and therefore, we did not attempt to determine an optimal verapamil and nifedipine dose for each patient. The results of the study may have been different if the dose of each calcium antagonist had been individualized, but the frequency and severity of adverse effects probably would have increased.

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Hemodynamic and Metabolic Effects of Diltiazem During Coronary Sinus Pacing with Particular Reference to Left Ventricular Ejection Fraction

MARTIN A. JOSEPHSON, MD, JAMES HOPKINS, BS, and BRAMAH N. SINGH, MD, Phil

To determine the systemic and coronary hemodynamic effects of diltiazem at rest and during pacing, 14 patients with stable angina pectoris undergoing coronary angiography were studied before and after 0.165 mg/kg (n = 7) and 0.25 mg/kg (n = 7) of intravenously administered diltiazem. Hemodynamic variables, metabolic measurements and left ventricular (LV) ejection fraction (EF) were obtained at rest and during coronary sinus (CS) pacing before and during diltiazem administration. Lactate production during control pacing turned into extraction after diltiazem ($p < 0.05$). At rest, systemic resistance was reduced by 21% ($p > 0.01$) and mean arterial pressure by 12% ($p < 0.01$); cardiac index increased from 2.4 ± 0.4 to 2.6 ± 0.4 liters/min/m^2 ($p < 0.01$), with no significant change in heart rate. The mean pulmonary artery pressure increased from 17 ± 2 to 19 ± 3 mm Hg ($p < 0.01$), but other hemodynamic variables were not affected. Diltiazem given during pacing reduced the mean aortic pressure (from 112 ± 15 to 104 ± 15 mm Hg, $p < 0.05$), but other hemodynamic variables were not affected significantly. LVEF decreased 16%, from 0.63 ± 0.9 to 0.53 ± 0.8 with CS pacing ($p < 0.01$); when the pacing was performed after diltiazem administration the 8% decrease in LVEF from 0.64 ± 0.09 to 0.59 ± 13 was less marked ($p < 0.01$). Diltiazem had no significant effect on LVEF at rest. The overall data suggest that the ischemic manifestations of CS pacing are attenuated by diltiazem in doses of the drug that exert no significant depressant effect on LV function in patients with coronary artery disease.

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Numerous studies confirm the antiischemic efficacy of calcium antagonists.[1–4] However, these compounds differ significantly in their chemical structure and in their overall pharmacologic properties.[1,5,6] The dihydropyridines such as nifedipine exert no sympatholytic effects, whereas verapamil and diltiazem have variable, noncompetitive sympathetic inhibitory actions.[5] The peripheral vasodilator potencies of these 3 compounds also differ somewhat.[1,5,6] Thus, such differences in their pharmacologic properties may be relevant to their actions in ameliorating myocardial ischemia. Extensive data have now accumulated on the acute systemic and coronary hemodynamic effects of verapamil[7–9] and nifedipine[10–11] in patients with coronary artery disease in relation to pacing-induced myocardial ischemia. Few data are available on the effects of diltiazem, although its effects in exercise-induced angina[3,12] and in variant angina[13–15] are well established. The present study was performed to study the antiischemic mechanisms of diltiazem by defining its intravenous effects on systemic and coronary hemodynamics and left ventricular (LV) ejection fraction (EF) at rest and during pacing-induced myocardial ischemia in patients who underwent coronary angiography.

From the Department of Cardiology, Wadsworth Veterans Administration Hospital and the Department of Medicine, UCLA School of Medicine, Los Angeles, California. This study was supported in part by grants from the Medical Research Service of the Veterans Administration, Washington, D.C.; the American Heart Association, Greater Los Angeles Affiliate, Los Angeles, California; and a Grant-in-Aid from Marion Laboratories, Inc., Kansas City, Missouri. Manuscript received August 6, 1984; revised manuscript received October 25, 1984, accepted October 29, 1984.

Address for reprints: Martin A. Josephson, MD, Department of Cardiology 691/111E, Wadsworth Veterans Administration Hospital, Wilshire and Sawtelle Boulevards, Los Angeles, California 90073.

Methods

Patient group: Fifteen men with clinically stable coronary artery disease who underwent cardiac catheterization were studied. All patients had exercise treadmill tests which were positive for ischemia. Seven patients had a history of myocardial infarction. Patients with myocardial infarction less than 3 months old, hypertension, renal or hepatic disease or evidence of congestive heart failure were excluded. Beta-blocking drugs, calcium channel-blocking drugs or long-acting nitrate medications were withdrawn 48 hours before the study. Significant coronary stenoses, defined as a 50% or greater di-

ameter reduction in a major coronary artery, were present in 1 patient with 1-vessel, 5 with 2-vessel and 9 with 3-vessel coronary artery disease (Table I). LVEF ranged from 0.47 to 0.75 (mean 0.61).

Catheterization: A No. 7Fr thermodilution pacing catheter (Wilton-Webster) was positioned in the coronary sinus (CS) near the great cardiac vein. The catheter location was confirmed by contrast injection and positioned to avoid placing the thermistor adjacent to major veins entering the CS, to obtain stable baseline flow curves and to allow CS blood withdrawal. A balloon flotation catheter was positioned in the pulmonary artery and a pigtail catheter in the central aorta.

Measurements: Pressures were measured for a complete respiratory cycle using fluid-filled catheter systems and Bell and Howell pressure transducers. Zero pressure was set at midchest level. Cardiac output by thermodilution was measured in duplicate using an Instrumentation Laboratory 701 cardiac output system. CS flow was measured in 10 patients by thermodilution[16] using an injectate of 5% dextrose infused at a rate of 56 ml/min. Blood oxygen saturation was determined with an OSM 2 Hemoximeter (Radiometer). Blood lactate levels were measured by the method of Apstein et al.[17] The percent myocardial lactate extraction was calculated as: A-V/A × 100, where A and V = respective arterial and CS lactate concentrations. Standard electrocardiographic leads I, aVF and V_5 were recorded throughout the procedure. Permanent copies of data for subsequent analysis were stored on paper using a Honeywell Visicorder system. Derived hemodynamic variables were calculated as: Stroke work index in g-m/m^2 = SI × ($\overline{AP}$ − $\overline{PCW}$) × 0.0136, where SI = stroke index, $\overline{AP}$ = mean aortic pressure and $\overline{PCW}$ = mean pulmonary capillary wedge pressure. Systemic vascular resistance in dynes s cm^{-5} = 80 × ($\overline{AP}$ − $\overline{RA}$)/CO, where $\overline{RA}$ = mean right atrial pressure and CO = cardiac output. Pulmonary vascular resistance in dynes s cm^{-5} = 80 × ($\overline{PA}$ − $\overline{PCW}$)/CO, where $\overline{PA}$ = pulmonary artery pressure.

Radionuclide imaging: Radionuclide ventriculograms were obtained after in vivo blood pool labeling with 25 mCi of technetium-99m pertechnitate. This method was shown to be highly reproducible in our laboratory.[18] Data were processed by a single observer and LVEF was determined as:

$$\text{LVEF} = \frac{\text{(end-diastolic counts)} - \text{(end-systolic counts)}}{\text{(end-diastolic counts)} - \text{(background counts)}}$$

Study protocol: Baseline measurements were made at least 20 minutes after completion of the diagnostic cardiac catheterization. These included heart rate, right atrial, pulmonary artery, pulmonary capillary wedge and aortic pressures, cardiac output, CS blood flow, aortic and CS blood oxygen and lactate content. LVEF was measured simultaneously with pressure measurements. CS pacing was initiated at a rate 25% above the heart rate at rest and increased by 10 beats/min every 3 minutes until angina or atrioventricular (AV) block occurred. Four patients described only mild (1+ of 4) angina during pacing at a rate of 110 beats/min and the pacing rate was increased by 10 beats/min. After administration of diltiazem, these patients could be paced to only 110 beats/min. All of these measurements were repeated during pacing at submaximal (average, 15 beats/min less than maximal rate) and maximal pacing rates and again 10 minutes after cessation of pacing. Diltiazem, 0.25 mg/kg, was administered intravenously over 2 minutes, followed by a maintenance infusion of 0.0014 mg/kg/min for the duration of the study. Because of the development of second-degree AV block during pacing in 5 of 7 patients, which prevented pacing to the maximal rate before diltiazem, the dose of diltiazem was subsequently reduced to a bolus of 0.165 mg/kg given over 5 minutes and a 0.001-mg/kg/min infusion. At this dosage, AV block during pacing occurred in 2 of 7 patients. All variables were measured again during administration of diltiazem and diltiazem-pacing conditions. Comparisons made between pacing before and after diltiazem administration were made at the identical, although not the maximal rate, for patients in whom AV block developed after diltiazem administration.

Statistical analysis: Data are presented as mean ± standard deviation. Comparisons were made using 2-tailed paired Student t test and the limit of significance was set at $p < 0.05$.

TABLE I Age and Coronary Angiographic Findings Relative to Ventricular Function in the Study Group

Pt	Age (yr)	LM (%)	LAD (%)	LC (%)	R (%)	LV	LVEF
1	53			60	70	N	0.62*
2	74		90	90	100	N	0.71*
3	70			70	90	N	0.71*
4	63		70	60	100	N	0.67*
5	58		70	70	100	Inf. H	0.50
6	56		70	70	100	Inf. A	0.47
7	62			70	100	N	0.75
8	54		90	60	100	N	0.61
9	58				100	Inf. H	0.61
10	52		100	70	100	Inf. H	0.60
11	56			60	99	Inf. H	0.57
12	68		60	70	100	N	0.66
13	61	60	50	60	100	Inf. H	0.62
14	43		100		100	N	0.63

* Determined by radionuclide ventriculography.
A = akinesia; H = hypokinesia; Inf. = inferior; LAD = left anterior descending artery; LC = left circumflex artery; LM = left main artery; LV = left ventriculogram; LVEF = left ventricular ejection fraction by contrast ventriculography (except where marked with an asterisk); N = normal; R = right coronary artery.

Results

Hemodynamic effects: The effects of intravenous diltiazem on measured and derived hemodynamic variables are shown in Table II. At rest, diltiazem caused a 12% decrease in mean arterial pressure ($p < 0.01$) and a 21% decrease in systemic vascular resistance ($p < 0.01$) without a significant effect on heart rate. In the 7 patients who received the larger dose of diltiazem, the average decrease in mean arterial pressure was 15%, compared with a 10% decrease in the 7 patients who received the smaller dose. Cardiac index increased 8% ($p < 0.01$). Pulmonary artery pressure increased 12% ($p < 0.01$) and pulmonary capillary wedge pressure increased 11% ($p < 0.01$), but no significant changes were seen in right atrial pressure, stroke work index or pulmonary vascular resistance.

During pacing, chest pain developed in 10 patients. After diltiazem therapy, during pacing to identical heart rates (which produced chest pain before diltiazem), chest pain was either absent or subjectively reduced in 9 of these 10 patients. During pacing, diltiazem caused a decrease of 7% in the mean arterial pressure ($p < 0.05$) without significantly affecting other measured hemodynamic variables. The effect of diltiazem on systolic and diastolic pressures and heart rate × systolic blood pressure are shown in Figure 1. Diltiazem reduced systolic pressure 7% at rest ($p < 0.01$) and 6% during pacing ($p < 0.01$), and diastolic pressure 13% at rest ($p < 0.01$)

TABLE II Systemic Hemodynamic Effects of Intravenous Diltiazem at Rest and During Coronary Sinus Pacing

	Rest		Pacing	
	Control	Diltiazem	Control	Diltiazem
Heart rate (beats/min)	69 ± 10	68 ± 10	118 ± 12	118 ± 12
Mean right atrial pressure (mm Hg)	8 ± 3	8 ± 3	8 ± 4	8 ± 3
Mean pulmonary artery pressure (mm Hg)	17 ± 2	19 ± 3*	18 ± 4	19 ± 4
Mean pulmonary capillary wedge pressure (mm Hg)	9 ± 2	10 ± 3†	11 ± 4	11 ± 4
Aortic pressure (mm Hg)				
Mean	101 ± 11	89 ± 12*	112 ± 15	104 ± 15†
Systolic	139 ± 17	129 ± 20*	141 ± 19	132 ± 19†
Diastolic	77 ± 10	67 ± 10*	89 ± 12	84 ± 10†
Cardiac index (liters/min/m^2)	2.4 ± 0.4	2.6 ± 0.4*	2.8 ± 0.4	2.8 ± 0.4
Stroke index (ml/m^2)	35 ± 7	39 ± 6*	24 ± 4	24 ± 5
Systemic vascular resistance (dynes s cm^{-5})	1,546 ± 318	1,219 ± 254*	1,498 ± 328	1,362 ± 283
Pulmonary vascular resistance (dynes s cm^{-5})	123 ± 30	127 ± 36	102 ± 29	118 ± 39
Stroke work index (g-m/m^2)	43 ± 10	41 ± 8	32 ± 8	30 ± 9

* $p < 0.01$; † $p < 0.05$, diltiazem compared with control values.

and 6% during pacing ($p < 0.05$). The decreases in heart rate × blood pressure product of 9% at rest and 7% during pacing did not reach statistical significance, because the heart rate was not significantly affected by diltiazem and remained constant during pacing.

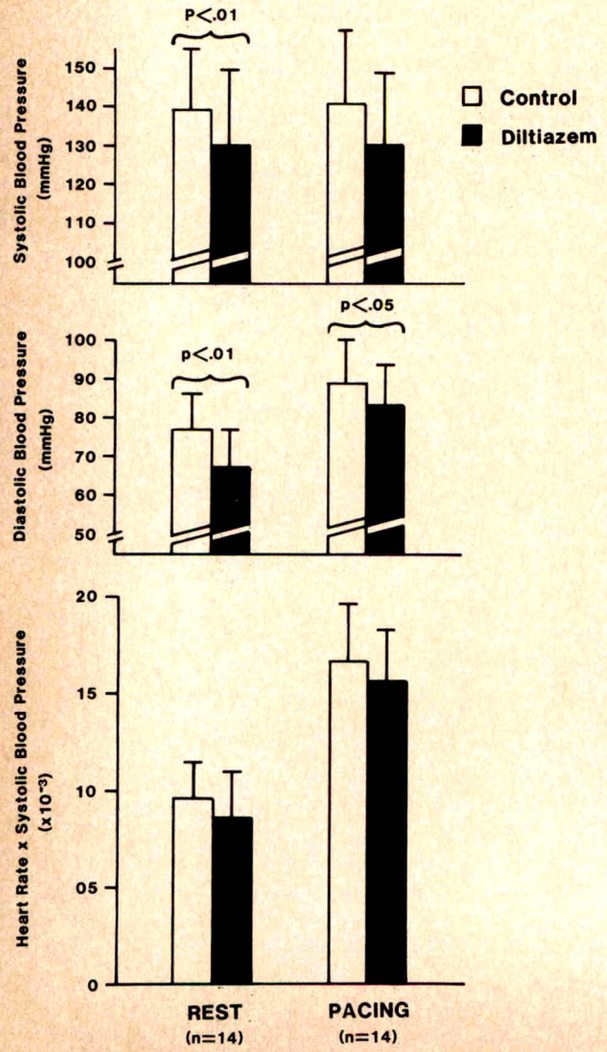

FIGURE 1. Effect of intravenous diltiazem on blood pressure and double product at rest and during coronary sinus pacing.

Effects of diltiazem on coronary flow and myocardial metabolism: The effects of diltiazem on coronary hemodynamics are listed in Table III. Pacing resulted in a 51% increase in CS flow and a 54% increase in myocardial oxygen consumption. There was no significant change in either of these parameters at rest or during pacing after diltiazem administration, although the measured myocardial oxygen consumption during pacing was reduced 11% (difference not significant). A significant increase in myocardial lactate extraction ($p < 0.05$) was seen after administration of diltiazem during pacing.

Effects of diltiazem on left ventricular ejection fraction: Figure 2 shows the effect of pacing on LVEF. The mean LVEF of 0.63 decreased 16% to 0.53 ($p < 0.01$) during pacing. Diltiazem had no effect on LVEF at rest (Fig. 2B). At rest after diltiazem, the LVEF was 0.64, not significantly different from its respective control value (0.63). During pacing after diltiazem administration, a significant 8% decrease ($p < 0.01$) in LVEF to 0.59 occurred, which was significantly higher than that of 0.53 during pacing at an identical mean heart rate before diltiazem administration ($p < 0.01$).

No significant adverse effects attributable to the administration of diltiazem developed during the study; however, AV nodal periodicity developed during CS pacing in 7 patients.

Discussion

This study demonstrates the beneficial effect of intravenous diltiazem in ameliorating the decrease in LVEF and other manifestations of ischemia induced by CS pacing in patients with coronary artery disease. LVEF is an objective and highly reproducible method for evaluating the effects of ischemia on ventricular function.[18,19] In the absence of coronary artery disease LVEF increases during atrial pacing.[20] No patient in our study had valvular or primary myocardial disease. Thus, the 16% reduction in LVEF after pacing in our patients must have been due to the development of myocardial ischemia. Other manifestations of pacing-induced ischemia include chest pain, changes in LV filling pressure, ST-segment changes and lactate production. Chest pain has been shown to be a nonspecific symptom with pacing, occurring with similar frequency in normal subjects and patients with coronary disease; the other

TABLE III Effects of Diltiazem on Coronary Hemodynamics at Rest and During Pacing

	CSF (ml/min)	MVO_2 (ml/min)	HRxBP ($\times 10^{-3}$)	MLEx (%)	
Control	96 ± 26	10.5 ± 3.2	9.7 ± 2.0	10.9 ± 19.1	
Diltiazem	101 ± 32	9.9 ± 2.3	8.8 ± 2.4	4.9 ± 28.6	
Pacing-control	145 ± 55	16.2 ± 5.7	16.7 ± 3.2	−1.8 ± 25.5	*
Diltiazem + pacing	146 ± 34	14.4 ± 3.0	15.5 ± 2.8	14.3 ± 8.7	*

* $p < 0.05$.
BP = systolic blood pressure; CSF = coronary sinus flow; HR = heart rate; MLEx = myocardial lactate extraction; MVO_2 = myocardial oxygen consumption.

parameters are more specific but quite insensitive as markers of ischemia when atrial pacing rates not exceeding 140 beats/min are used.[20] In our study, pacing rates higher than 140 beats/min were precluded by AV nodal conduction. The effect of diltiazem on LVEF occurred coincident with a 7% decrease (difference not significant) in heart rate × blood pressure product. Such an effect might be expected to decrease myocardial oxygen demands and reduce the ischemic ventricular dysfunction.

Although a reduction in myocardial oxygen demand is believed to be the predominant mechanism by which diltiazem[12] and other calcium antagonists[9,11,21,22] act in ischemia induced by pacing or exercise, other contributing mechanisms cannot be discounted. For example, in the study by Petru et al,[12] oral diltiazem did not affect heart rate × blood pressure product at peak exercise. Although there was no difference in the gross determinants of myocardial oxygen consumption, LVEF at peak exercise was 18% higher (0.52 vs 0.44, $p < 0.01$) during diltiazem therapy. Additionally, there was no difference in either end-systolic or end-diastolic volumes. Thus, other potential mechanisms of action of diltiazem, such as improved myocardial perfusion and reduction in oxygen demand due to improved ventricular compliance, must be considered.

Diltiazem has improved myocardial blood flow to ischemic regions in a variety of animal models.[23,24] CS flow was unchanged after diltiazem therapy in our study when myocardial oxygen demands were decreased, although diltiazem decreased coronary resistance 18% at rest and 9% during pacing. Data from other studies on coronary flow with calcium antagonist therapy have been variable. For example, nifedipine has been shown to increase CS flow relative to myocardial oxygen consumption.[11,25] Studies with verapamil have shown either no change[26] or a decrease[27] in CS flow. Small changes in regional myocardial flow that might be significant may not be detectable in the more global measurement of CS flow assessed by thermodilution. Verapamil decreases the cross-sectional area of stenosis by 13%[26]; similar effects have been shown with diltiazem,[28]

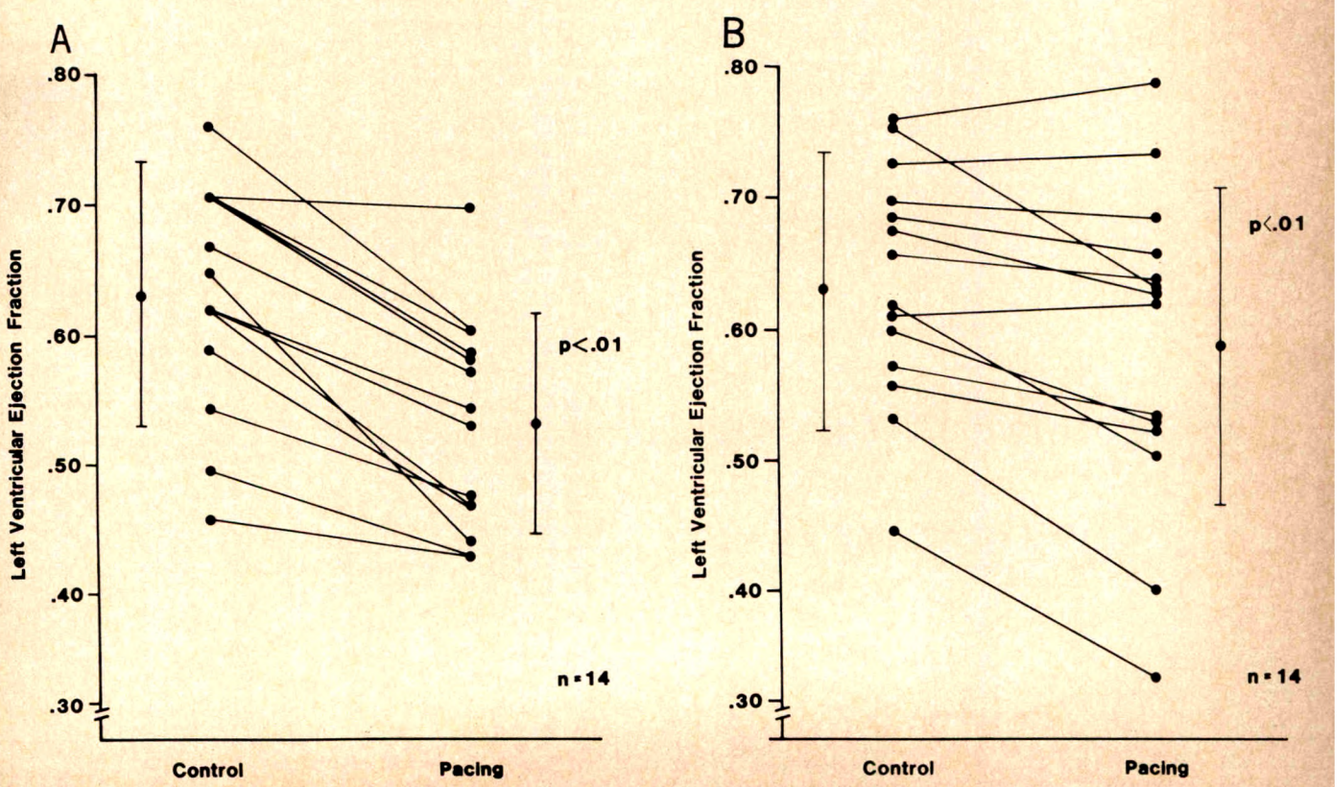

FIGURE 2. A, radionuclide left ventricular ejection fraction at rest and during coronary sinus pacing. **B,** effect of diltiazem on left ventricular ejection fraction at rest and during coronary sinus pacing.

suggesting an additional mechanism through an improvement in myocardial perfusion. Furthermore, from analogy to the overall actions of verapamil,[29] a component of the antianginal action of diltiazem may be attributable to its favorable effect on the diastolic properties of the ischemic myocardium. However, this presumed action of the drug requires investigational verification.

Our data are of interest from the standpoint of the hemodynamic effects of diltiazem in patients with coronary artery disease. In doses between 0.165 and 0.25 mg/kg given intravenously, diltiazem produced somewhat smaller reductions in systemic vascular resistance than either verapamil[1,9] or nifedipine[10,11] in patients with relatively normal EFs. The small increase in the induced pulmonary capillary wedge pressure after diltiazem probably results from a reduction in myocardial contractility. Because cardiac and stroke volume indexes increased and LVEF was unchanged after diltiazem therapy, the depressant effect of diltiazem on myocardial contractility is offset by the peripheral effects of this drug. These changes are more akin to those induced by verapamil than by nifedipine, which is the most potent peripheral vasodilator of the 3 compounds and exerts the most striking reflex effects on contractility. This finding appears to be reflected particularly in the changes induced by 3 compounds in LVEF. For example, verapamil usually produces no change in LVEF,[21] and diltiazem produces either no change or a slight increase as found in our studies with significant increases that occurred when sublingual or single oral doses of nifedipine were given.[30] The overall comparative data indicate the varying propensity of the 3 compounds in affecting myocardial contractility. However, our data do not exclude the possibility that, as with verapamil,[31] diltiazem may produce depression of ventricular performance in patients with imparied ventricular function especially at large doses.

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Familial Aggregation and Early Expression of Hyperapobetalipoproteinemia

ALLAN SNIDERMAN, MD, BABIE TENG, MSc, JACQUES GENEST, MD, KATHERINE CIANFLONE, BSc, SHOLOM WACHOLDER, PhD, and PETER KWITEROVICH Jr., MD

Family history is an important predictor of coronary risk. However, this relation, in large part, is not explained by the known risk factors such as systemic hypertension or hyperlipidemia. In the present study, plasma lipid, lipoprotein lipid, and plasma low-density lipoprotein (LDL) apoB levels were measured in 66 offspring (myocardial infarction [MI] offspring) of 24 families in which an index parent had premature coronary artery disease and hyperapobetalipoproteinemia. These results were compared to those obtained in 207 control children and young adults. Univariate analysis revealed that plasma LDL apoB and all other lipid and lipoprotein levels except high-density lipoprotein cholesterol were significantly higher in the MI offspring. Multivariate analysis showed plasma LDL apoB and LDL cholesterol best differentiated the MI offspring from control children and young adults. Of the 66 children, 22 had hyperapobetalipoproteinemia, of whom only 7 had clearly abnormal LDL cholesterol or plasma triglyceride levels. Thus, a substantial portion of children born to a parent with premature coronary artery disease and hyperapobetalipoproteinemia have the same disorder of lipoprotein metabolism.

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There is little doubt that the plasma lipoproteins significantly influence the risk of coronary artery disease (CAD). However, this relation is complex with, on the one hand, risk increasing as low-density lipoprotein (LDL) levels increase, but on the other, decreasing as high-density lipoprotein (HDL) levels increase.[1,2] To this long-standing epidemiologic network of evidence can now be added the recent demonstration that appropriate dietary and pharmacologic therapy significantly decreases the incidence of CAD death rate and myocardial infarction (MI) in patients with type II hyperlipoproteinemia.[3]

Even though most patients with premature CAD have LDL cholesterol levels within the normal range, this does not mean their LDL is always normal. LDL are complex particles with the principal lipid, cholesterol ester, sequestered in a core surrounded by a surface layer made up of cholesterol, phospholipid and the major protein in LDL—apoB.[4] Until recently, the plasma concentration of LDL was usually expressed only by its cholesterol content. But this practice provides incomplete information. For example, we observed that although most patients with premature CAD have normal LDL cholesterol levels, many have elevated LDL apoB values—a combination we called hyperapobetalipoproteinemia.[5] And indeed, several studies indicate that apoprotein levels do identify patients at high risk of CAD more clearly than do lipid levels.[5–15]

Although lipoprotein cholesterol levels clearly modulate risk for individuals another body of evidence points to the aggregation of CAD within families, and this phenomenon apparently cannot be completely explained by the factors known to affect coronary risk.[16–18] Therefore the purpose of this study was to examine the plasma lipids, lipoprotein lipids, and plasma LDL apoB levels in children of families where 1 parent had both premature CAD and hyperapobetalipoproteinemia. These data were then compared with those from 3 unrelated control groups of children and young adults to determine whether familial aggregation

From the Cardiovascular Research Unit, Department of Medicine, Royal Victoria Hospital; The Department of Epidemiology, McGill University, Montreal, Canada; Departments of Pediatrics and Medicine, Lipid Research–Atherosclerosis Unit, The Johns Hopkins University School of Medicine, Baltimore, Maryland. This study was supported by March of Dimes Defect Foundation: Contract No. 1-HV1-2158; Medical Research Council of Canada MA-5480; National Heart, Lung, and Blood Institute Grant CRC-RR-52, Pediatric Clinical Research Center, Program of the Division of Research Resources, and Grant HL-18574, National Institutes of Health.

Address for reprints: Allan Sniderman, MD, Cardiovascular Research Unit, Room M4.14, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec H3A 1A1, Canada.

TABLE I Plasma Total Lipid, Lipoprotein Cholesterol and Plasma Low-Density Lipoprotein ApoB Levels in Offspring of Patients with Hyperapobetalipoproteinemia and Myocardial Infarction and Unrelated Control Groups

	MI Offspring	C 1+2+3	C1	C2	C3
TC (mg/dl)	174 ± 34†	164 ± 27	172 ± 19	150 ± 31	164 ± 29
Tg (mg/dl)	103 ± 58‡	81 ± 32	83 ± 21	87 ± 44	78 ± 32
LDL C (mg/dl)	103 ± 33*	93 ± 27		92 ± 30	93 ± 27
HDL C (mg/dl)	51 ± 13	52 ± 11		40 ± 8	56 ± 9
LDL apoB (mg/dl)	110 ± 36‡	82 ± 18	80 ± 16	73 ± 24	87 ± 14

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.0001$.
C1, C2, C3 = control groups 1, 2 and 3; HDL C = high-density lipoprotein cholesterol; LDL apoB = low-density lipoprotein apoB; LDL C = LDL cholesterol; MI offspring = children of affected parents; TC = total plasma cholesterol; Tg = total plasma triglyceride.

of hyperapobetalipoproteinemia is present within the offspring of the index cases.

Methods

Study groups: *Children of affected parents:* The children of affected parents (MI offspring) consisted of children in 24 families in which 1 parent had both a documented MI before the age of 55 years and hyperapobetalipoproteinemia. All index parents but one were male. Their average age was 48 ± 8 years (mean ± standard deviation) and all had hyperapobetalipoproteinemia, that is, the plasma LDL apoB level was at least 120 mg/dl and the LDL cholesterol was at least 200 mg/dl. Fasting plasma samples were obtained from 66 children and young adults in these families, representing 84% of the total number of offspring. The average age of those studied was 17 ± 7 years (range 3 to 31). Thirty-one were male and 35 were female subjects.

Control groups: Three unrelated groups of children and young adults were studied. Group C1 consisted of 62 healthy Montreal children from whom plasma samples were obtained at a routine health examination. Their average age was 11.6 ± 8 years (range 4 to 23). Twenty-eight subjects were male and 34 were female. Group C2 consisted of 40 children in grade 10, all males, sampled as part of a larger project to determine community lipid and lipoprotein values. These children live in a small Pennsylvania city and their age was 16 ± 1 years. Group C3 consisted of 105 medical students at The Johns Hopkins University with an average age of 20.8 ± 1.5 years (range 19 to 30 years). Ninety subjects were male and 15 were female.

Laboratory methods: After a fast of 12 hours, blood samples were obtained in tubes containing EDTA (1 mg/ml) and plasma then separated by centrifugation. Plasma total cholesterol and triglyceride were measured enzymatically. HDL cholesterol was determined in the supernatant after precipitation of the apoB containing lipoproteins by heparin and manganese chloride.[19] In the MI offspring, LDL was isolated by preparative ultracentrifugation between density 1.006 to 1.063 g/ml.[5] That is, the density <1.006 lipoproteins were first removed and then LDL isolated after a second ultracentrifugation at density 1.063 g/ml. In groups C2 and C3, LDL cholesterol was determined using the methods of the Lipid Research Clinic.[19] Plasma LDL apoB was measured in all groups by radial immunodiffusion.[20] In groups MI, C1 and C3, this was done at the Royal Victoria Hospital laboratory using a 1.5% agarose gel read at 18 hours. In groups C2, radial immunodiffusion was performed at The Johns Hopkins laboratory using a 2% agarose gel read at 72 hours. The measurements in the 2 techniques agree closely (r = 0.96).

Normal limits for plasma lipids and lipoprotein lipids were based on the Lipid Research Clinics Prevalence Study.[21] The upper limit, based on our previous studies in adults for plasma LDL apoB, was fixed at 120 mg/dl.

Groups were compared initially with *t* tests with the data then adjusted for age and sex effects by analysis of covariance. Multiple logistic regression was then employed to search for the most informative parameters.[22]

Results

The means and standard deviations for all measurements are summarized in Table I. Each of the 3 control groups is listed separately and these values are averaged to provide an overall mean for the control group. The values for the MI offspring were then compared with those of the overall control group.

First, a univariate comparison was carried out using an unpaired *t* test. This revealed that plasma total cholesterol, total triglyceride, and plasma LDL apoB levels were all significantly higher in the MI offspring than in the control group. By contrast, the mean HDL cholesterol levels did not differ significantly between these 2 groups. The influence of age and sex was next considered, and these factors were determined in the control group with all data then adjusted by analysis of covariance. This altered the absolute differences between the groups only slightly and the differences noted above remained just as significant.

Multivariate analysis was then undertaken by multiple logistic regression: plasma LDL apoB was the parameter selected first as significant with LDL cholesterol identified next. Addition of the 3 other lipid variables did not substantially improve the fit. Thus, multivariate analysis identified plasma LDL apoB and then LDL cholesterol as the measurements that permit best separation of the MI offspring and control group.

These differences can also be appreciated by comparing the difference between the means of the control and MI offspring of a given measurement as a fraction of the control standard deviation. Thus, the mean for plasma total cholesterol in the MI offspring differs from the mean in the control offspring by much less than 1 standard deviation. This is also the case for LDL cholesterol, while the difference is only a bit larger (0.62) for triglyceride. By contrast, there is a much larger difference between the 2 groups for plasma LDL apoB. In this instance, the difference is 1.5 times the control standard deviation. So that the magnitude of difference

between the 2 groups for LDL cholesterol and LDL apoB can readily be seen, histograms for these 2 variables are shown in Figure 1.

Table II lists the persons in the MI offspring with elevated plasma LDL apoB. The youngest was 4 years old, a boy, and the oldest was 33 years old, a woman. Of these 22, 4 had LDL cholesterol values above the 95th percentile for age and sex and, thus, would be recognized as abnormal; 2 others were just at this limit. One young adult with an increased LDL cholesterol also had an elevated plasma triglyceride level, whereas 3 others had increased plasma triglyceride, but normal LDL cholesterol levels; 2 had plasma triglyceride levels at the 95th percentile. Thus, only 7 of the 22 had clearly abnormal lipid levels; the rest, were it not for plasma LDL apoB, would have been conventionally characterized as normal.

Discussion

This study examines children and young adults in families where a parent had both suffered a premature MI and had hyperapobetalipoproteinemia. Many of the offspring also have hyperapobetalipoproteinemia; that is, they had elevated LDL apoB levels in the face of a normal LDL cholesterol. Only a few had elevated LDL cholesterol or plasma triglyceride levels, and thus measurement of plasma and lipoprotein lipid variables did not clearly identify many persons within the MI offspring as being different from the 3 control groups of children and young adults. By contrast, measurement of plasma LDL apoB differentiated the primary study group from the 3 control groups, also identified the few children with elevated LDL cholesterol, but more importantly, identified the larger number with hyperapobetalipoproteinemia.

Familial aggregation of CAD has been demonstrated repeatedly. The Western Collaborative Study[23] revealed a significant link between the history of CAD and parental history of CAD; while Slack and Evans showed a several-fold excess mortality in the relatives of index cases with CAD compared to the normal population.[24]

Nevertheless, the connection between familial aggregation of CAD and familial aggregation of lipids is clearly imperfect.[16–18] More recently, however, the relation of apoproteins to risk of CAD has been examined. Although most patients with premature CAD are normocholesterolemic,[5,25] there is now considerable agreement that, on average, apoB levels are higher and $apoA_1$ (the major apoprotein in HDL) levels lower in patients with CAD than in those without disease.[5–15] Nevertheless, all such studies on the relation of apoprotein levels to atherosclerosis have been cross-sectional since the presence or absence of disease was related to concurrent lipid and apoprotein levels. Therefore, the apoprotein abnormalities observed may have been simply a consequence, rather than a precursor, of vascular disease. The present data indicates that hyperapobetalipoproteinemia is expressed in families with premature CAD long before the usual age when clinical symptoms begin, and therefore contributes strongly to the hypothesis that this metabolic disorder may well be important in the pathogenesis of CAD. Our hypothesis is further strengthened by the results of Kukita et al,[26] who reported that apoB levels in first-degree adult relatives of patients with angiographically diagnosed CAD were significantly higher than those in age- and sex-matched control subjects.[26]

Even though a child as young as 4 years was affected, most of those with hyperapobetalipoproteinemia were beyond puberty, and thus it is possible that this disorder is not fully expressed until young adulthood. In the present study, the control groups were chosen not only to bracket the age range in the primary study group, but

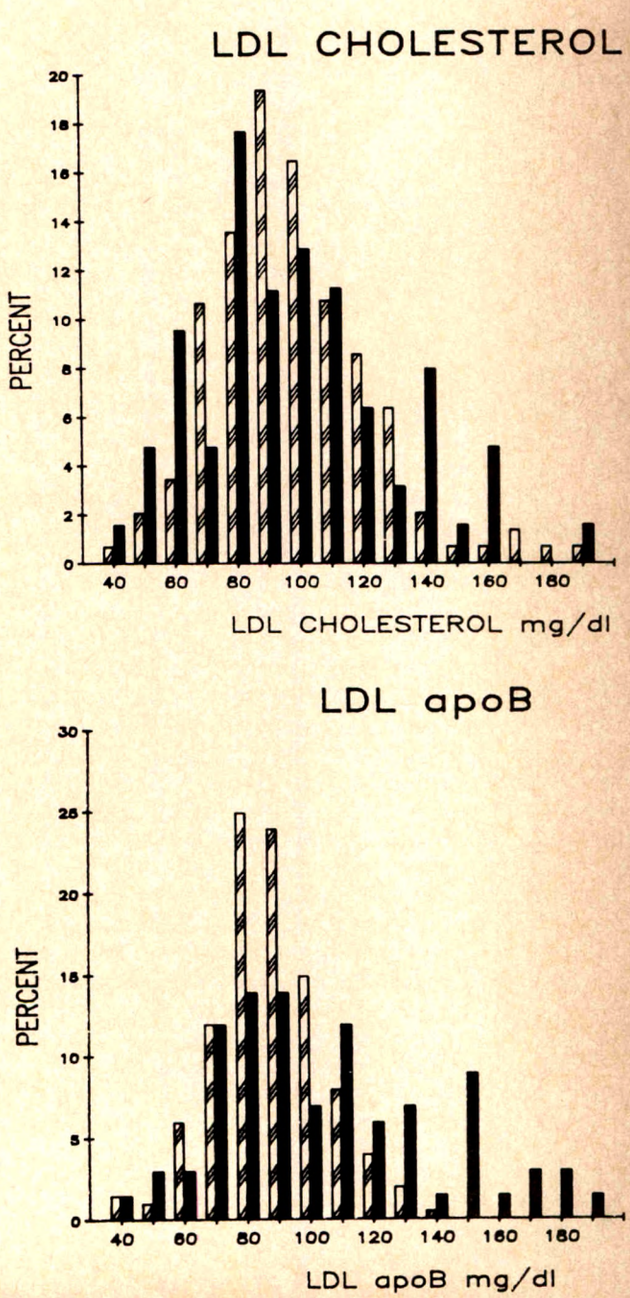

FIGURE 1. Low-density lipoprotein (LDL) cholesterol and LDL apoB levels for both the control group (**hatched bars**) and the children of affected parents (**solid bars**).

TABLE II Children of Affected Parents with Elevated Plasma Low-Density Lipoprotein ApoB Levels

Age (yr) & Sex	Tg	TC	LDL apoB	LDL C	HDL C
4M	42	180	137	130	40
14F	184 (131)	216	155	120	54
22M	198 (165)	242	129	148 (147)	61
25F	181 (172)	189	153	132	29
23F	157	224	205	165 (159)	43
19F	145	210	195	141	31
22M	183	206	130	148 (147)	32
21F	98	267	175	215 (164)	32
17F	94	210	121	162 (137)	26
8M	101 (101)	182	124	120	40
12F	86	217	139	159 (136)	46
11F	25	196	155	113	68
11F	60	200	128	113	75
25F	133	221	190	148	43
23F	152	217	160	123	64
19F	97	177	142	116	45
25M	95	137	131	77	40
20F	169 (165)	180	154	103	47
26M	173	190	138	106	54
27M	179	234	153	169 (165)	32
26F	402 (172)	240	170	104	56
27F	139	197	154	126	43

Figures in parentheses are the 95th percentile of age and sex values based on the Lipid Research Clinics Survey.

All values are in milliliters per deciliter.

HDL C = high-density lipoprotein cholesterol; LDL apoB = plasma low-density (LDL) apoB; LDL C = LDL cholesterol; LP = lipoprotein phenotype; TC = total plasma cholesterol; Tg = plasma triglyceride.

also to be from different geographic sites so as to make them more likely a representative of Canadian and American norms at these ages.

The physiochemical basis for the disproportionate increase in LDL apoB compared to LDL cholesterol characteristic of hyperapobetalipoproteinemia is now clear. Even in normal persons, LDLs are heterogeneous particles differing in size and cholesterol content but with a constant amount of protein per particle. The larger LDL particles are thus less dense and contain more core cholesterol, but relatively less protein; the converse is the case for smaller LDL particles. In hyperapobetalipoproteinemia, the number of LDL particles is above normal, but the cholesterol level is not proportionately elevated because most of the particles are smaller and denser, depleted in cholesterol ester and relatively enriched in protein.[27]

Although in no way established, it is possible that the familial aggregation of hyperapobetalipoproteinemia evident in the present study may to an important degree, be genetic, and this, obviously, is an important hypothesis to pursue. Of the lipoprotein disorders associated with premature CAD, familial hypercholestrolemia is best characterized, but accounts for only a small portion, about 5%, of the premature CAD seen clinically. Another disorder, familial combined hyperlipidemia, first described in 1973, has been found in a higher proportion, from 10 to 20%, of patients with premature CAD.[28] Familial combined hyperlipidemia is characterized by the presence of multiple lipoprotein phenotypes within a family, but it has now been shown that there is a common denominator linking these various phenotypes—an elevated total plasma apoB.[29] Thus, there may be considerable, although not complete, homology between hyperapobetalipoproteinemia and familial combined hyperlipidemia.[30]

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Continuous Positive Airway Pressure by Face Mask in Acute Cardiogenic Pulmonary Edema

JUKKA RÄSÄNEN, MD, JUHANI HEIKKILÄ, MD, JOHN DOWNS, MD, PERTTI NIKKI, MD, IRMA VÄISÄNEN, MD, and ANNE VIITANEN, MD

The therapeutic efficacy of continuous positive airway pressure (CPAP) administered by face mask was studied in 40 patients with acute cardiogenic pulmonary edema and respiratory failure. Arterial blood gas values and pH, systemic arterial pressure, heart rate and respiratory rate were measured during administration of 30% oxygen with a high-flow face mask apparatus at ambient airway pressure. Twenty patients were then randomly chosen to continue ambient airway pressure breathing and 20 received 10 cm H_2O of CPAP. The measurements were repeated 10, 60 and 180 minutes after therapy was initiated. During the first 10 minutes of CPAP treatment, arterial blood oxygen partial pressure increased 8 ± 9 mm Hg (mean ± 1 standard deviation), ($p < 0.01$) and respiratory rate decreased 5 ± 5 breaths/min ($p < 0.001$). Systolic arterial pressure decreased 12 ± 21 mm Hg ($p < 0.05$), and heart rate by 10 ± 11 beats/min ($p < 0.001$). A decrease in respiratory rate by 2 ± 5 breaths/min ($p < 0.05$) was the only change that occurred in the control group. The improvement in arterial blood oxygenation persisted throughout the investigation period ($p < 0.05$). Thirteen patients (65%) in the control group and 7 patients (35%) in the CPAP group met our criteria for treatment failure during the study ($p = 0.068$). Thus, CPAP administered by face mask improves gas exchange, decreases respiratory work, unloads circulatory stress, and may reduce the need for ventilator treatment in acute cardiogenic pulmonary edema.

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Continuous positive airway pressure (CPAP) is known to improve arterial blood oxygenation in acute respiratory failure of both cardiac[1–3] and noncardiac[4] origin. It also may decrease the work of spontaneous breathing by improving lung mechanics.[3,5,6] CPAP is usually combined with mechanical ventilation and applied to the patient through an endotracheal tube. However, the complications of endotracheal intubation and ventilator treatment[7] may be particularly hazardous in patients with heart disease and acute pulmonary edema. Elevated airway pressure also can be administered with a tight-fitting face mask to patients who do not require endotracheal intubation for mechanical ventilation or for airway support.[8,9] The use of a face mask for CPAP in cardiogenic pulmonary edema has been described previously,[1,3] but its efficacy has not been tested prospectively. This investigation determines whether cardiopulmonary function could be improved and ventilator treatment avoided by applying CPAP with a mask to patients with acute cardiogenic pulmonary edema.

From the Department of Anesthesiology and the First Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland, and the Department of Anesthesiology, Northwestern University, Chicago, Illinois. Manuscript received July 18, 1984; revised manuscript received October 30, 1984, accepted October 31, 1984.

Address for reprints: Jukka Räsänen, MD, Mobile ICU/PPKL, Helsinki University Central Hospital, Haartmaninkatu 4, 00290 Helsinki 29, Finland.

Methods

Patients: The study group consisted of 40 patients with respiratory failure and clinical and radiologic evidence of acute, alveolar pulmonary edema of cardiac origin. The diagnostic criteria of respiratory failure were dyspnea, signs of increased respiratory work such as intercostal and suprasternal retractions or use of accessory respiratory muscles during inspiration, a respiratory rate of more than 25 breaths/min or arterial blood oxygen partial pressure (PaO_2) to inspired oxygen concentration ratio of less than 200. We excluded patients who were unresponsive to speech, those unable to maintain patent airway, and those who had signs of lung infection, evidence of pulmonary embolism, or chronic lung disease with carbon dioxide retention at rest. Relevant data concerning clinical features and medical treatment are listed in Table I. All patients had severe heart failure primarily after acute myocardial infarction (n = 19) or acute exacerbation of chronic left ventricular dysfunction (n = 19). The study was started immediately after the clinical diagnosis had been made.

Continuous positive airway pressure device: A high-flow, venturi-powered face mask apparatus (Vital Signs)

similar to one described earlier[10] was used for spontaneous breathing in all patients. CPAP was achieved by attaching a threshold resistor valve to the mask. The opening pressure of the valve was checked before use. When the valve was not in place, the airway pressure was ambient. The venturi was connected to a high-pressure oxygen source with its entrainment orifice open to room air. Because the entrained air was not enriched with oxygen, the inspired oxygen concentration was 28 to 30%, depending on the entrainment ratio of the particular venturi in use. Room air entrainment assured that the inspired oxygen concentration was unaffected by changes in flow rate and airway pressure. Therefore, it remained constant throughout the study. The flow rate was adjusted to keep the exhalation valve open throughout the respiratory cycle, thus ensuring a nearly constant airway pressure.

Experimental protocol: One of the investigators or the anesthesiologist on call in the intensive care unit evaluated patients for potential inclusion in the study, supervised the respiratory therapy and recorded the results of the measurements. After initiation of the investigation, all patients breathed with the face mask apparatus with an ambient airway pressure for 5 minutes. Then, baseline heart rate, respiratory rate, blood pressure and results of arterial blood analyses were recorded. Patients then were randomly assigned to 1 of 2 groups by opening 1 of 40 sealed envelopes containing instructions for the use of either ambient airway pressure (control group, n = 20) or 10 cm H_2O CPAP (CPAP group, n = 20). Cardiopulmonary measurements were repeated after 10, 60 and 180 minutes of group specific therapy. Heparinized arterial blood was analyzed for pH, Pa_{O_2}, and carbon dioxide partial pressure (Pa_{CO_2}) within 5 minutes of sampling (ABL-2, Radiometer). The study was interrupted after a 10-minute trial of the assigned treatment if any of the following criteria were met: Pa_{O_2} <50 mm Hg, Pa_{CO_2} >55 mm Hg or respiratory rate >35 breaths/min. The time of the study then was recorded and the patient classified as a failure of the assigned treatment. Subsequent respiratory therapy in these patients was determined by the physician in charge. Loss of consciousness or airway obstruction were indications for endotracheal intubation and ventilatory assistance at any time. Medical treatment of pulmonary edema was not restricted. Airway pressure and inspired oxygen concentration were not changed during the data collection period. Need for ventilator treatment after the study and final outcome were determined from medical records after patients left the hospital.

The study protocol was approved by the Committees on Ethics of the Department of Anesthesiology and of the First Department of Medicine at Helsinki University Central Hospital.

Data analysis: Baseline cardiopulmonary data of the groups were compared using the Student *t* test for means of independent samples. The 10-minute and 3-hour cardiopulmonary responses to therapy were analyzed separately. Data from all patients were included when the response to the first 10 minutes of therapy was analyzed. The Student *t* test for paired observations was used to detect significant differences within groups. Responses of the groups to treatment were compared using the Student *t* test for means of independent samples. Changes over the entire study period were analyzed only if patients maintained spontaneous respiration throughout the 3-hour study. A 1-way repeated measures analysis of variance was then used to detect changes within the groups. Responses of the groups to treatment were compared with a 2-way repeated measures analysis of variance. The percentage of patients that maintained spontaneous breathing during the study was plotted as a function of time in both groups using the life-table method. The curves so constructed were compared with the Mantel-Cox test. The differences in mortality and in the frequency of ventilator treatment were compared with the Fisher's exact test.

TABLE I Clinical Features and Medical Treatment of the Patient Series*

	Control (n = 20)	CPAP (n = 20)
Age (yr)	73 ± 9	74 ± 9
Men/women	7/13	6/14
Underlying cause of pulmonary edema		
Myocardial infarction	10	9
Chronic heart failure	9	10
Acute aortic valve incompetence	0	1
Ventricular arrhythmia	1	0
Cardiothoracic ratio	0.62 ± 0.06	0.60 ± 0.08
Medical treatment†		
Furosemide (mg)	41 ± 18	53 ± 29
Morphine (mg)	7 ± 3	8 ± 4
Diazepam (mg)	9 ± 5	6 ± 3
Chlorpromazine (no. of pts)	10	9
Nitroglycerin (no. of pts)	4	1
Nitroprusside (no. of pts)	3	3
Digitalis (no. of pts)	6	8
Dopamine (no. of pts)	4	4
Dobutamine (no. of pts)	0	1
Urine output (ml/3 hr) (mean ± SD)	918 ± 461	766 ± 575

* Differences not statistically significant.
† Cumulative doses of furosemide, morphine and diazepam were calculated starting 6 hours before and ending 3 hours after randomization. The use of inotropic drugs or vasodilators was taken into account if these drugs were given within 3 hours of randomization.
CPAP = continuous positive airway pressure; SD = standard deviation.

Results

The control and CPAP groups were found to be comparable with regard to age, gender, underlying cause of pulmonary edema, medical treatment and cardiothoracic ratio (Table I). All patients maintained spontaneous respiration for the first 10 minutes of the study. Seven patients in the control group and 13 patients in the CPAP group completed the investigation. Twenty patients met our criteria for failure of assigned treatment. No technical problems were associated with either treatment, nor were there any complications related to the face mask such as nasal bridge pain, gastric dilatation or aspiration.

Pulmonary function: Upon inclusion in the study, all patients had moderate to severe respiratory failure. The respiratory rate ranged from 11 to 47 breaths/min, Pa_{O_2} from 31 to 74 mm Hg and Pa_{CO_2} from 24 to 76 mm Hg (Table II).

The respiratory rate of patients in the control group decreased slightly ($p < 0.05$) during the first 10 minutes of treatment with an ambient airway pressure. The arterial P_{O_2}, P_{CO_2} and pH remained unchanged. When CPAP was applied, Pa_{O_2} increased 8 ± 9 mm Hg ($p < 0.01$). Simultaneously, the respiratory rate decreased ($p < 0.001$) as did the Pa_{CO_2} ($p < 0.01$). Clinically, the use of CPAP frequently improved the patient's breathing pattern, decreased intercostal and suprasternal retractions, and relieved subjective respiratory distress. The response of arterial blood oxygenation to the first 10 minutes of therapy was significantly different in the 2 groups ($p < 0.001$). This difference persisted over the entire 3-hour investigation period ($p < 0.05$) (Fig. 1). The

TABLE II Changes in Cardiopulmonary Variables During 10 Minutes of Breathing with an Ambient (Control [n = 20]) or Continuous Positive Airway Pressure (n = 20)

Time (min)		0	10
Respiratory rate (breaths/min)	Control	30 ± 8	28 ± 7*
	CPAP	29 ± 8	24 ± 7†
Pa_{O_2} (mm Hg)	Control	52 ± 10	52 ± 9
	CPAP	52 ± 9	60 ± 9‡,§
Pa_{CO_2} (mm Hg)	Control	38 ± 9	37 ± 7
	CPAP	41 ± 12	39 ± 10‡
Arterial blood pH	Control	7.36 ± 0.10	7.38 ± 0.08
	CPAP	7.33 ± 0.10	7.35 ± 0.07*
Heart rate (beats/min)	Control	102 ± 20	105 ± 18
	CPAP	113 ± 25	103 ± 23†,‖
Systolic arterial pressure (mm Hg)	Control	145 ± 37	142 ± 29
	CPAP	133 ± 33	121 ± 24*
Diastolic arterial pressure (mm Hg)	Control	82 ± 16	82 ± 16
	CPAP	80 ± 19	75 ± 15*
Rate-pressure product/100 (mm Hg × beats/min)	Control	145 ± 37	149 ± 27
	CPAP	151 ± 53	124 ± 35‡,‖

* $p < 0.05$ within 1 group; † $p < 0.001$ within 1 group; ‡ $p < 0.01$ within 1 group; § $p < 0.001$ between the responses of the groups; ‖ $p < 0.01$ between the responses of the groups.
All values are expressed as mean ± standard deviation.
CPAP = continuous positive airway pressure.

respiratory rate decreased progressively and the arterial pH increased even though Pa_{CO_2} remained unchanged in both groups (Table III).

Cardiovascular function: Baseline systolic arterial pressure ranged from 70 to 220 mm Hg and heart rate from 64 to 155 beats/min. Patients who received CPAP had a slightly lower systolic blood pressure and higher heart rate than those in the control group (difference not significant [NS]) (Table II).

No circulatory changes were noted in the control group during the first 10 minutes of therapy. The use of CPAP was associated with a decrease in heart rate ($p < 0.001$), blood pressure ($p < 0.05$) and rate-pressure product ($p < 0.01$). The changes in heart rate and rate-pressure product differed significantly between the 2 groups ($p < 0.01$). A decrease in an initially low systolic blood pressure (110 mm Hg or lower) was seen on 1 of 4 occasions in the control group and on 3 of 8 occasions in the CPAP group (NS). During the 3-hour follow-up, arterial pressure decreased significantly in both groups, but the heart rate and the rate-pressure product decreased only in the patients who received CPAP (Table III).

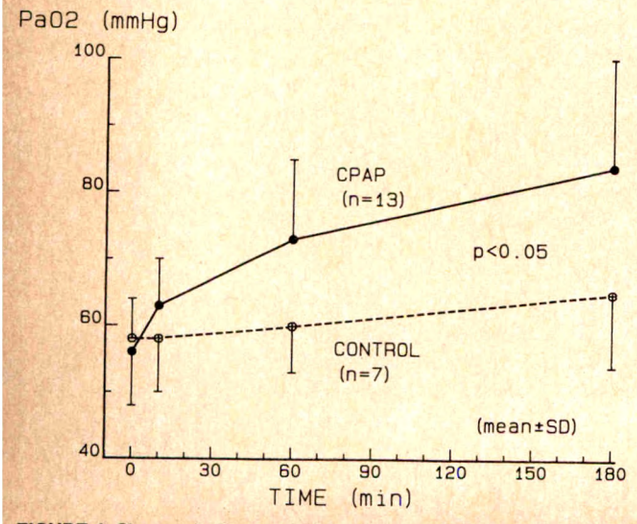

FIGURE 1. Changes in the arterial blood oxygen partial pressure (Pa_{O_2}) over the 3-hour observation period in 7 patients breathing with an ambient airway pressure and in 13 patients receiving 10 cm H_2O continuous positive airway pressure (CPAP). SD = standard deviation.

Clinical course: On inclusion in the study, 12 patients in the control group and 10 patients in the CPAP group met the criteria for treatment failure. After 10 minutes of group specific therapy, 3 of the 12 patients who breathed with an ambient airway pressure and 5 of the 10 who received CPAP improved and remained in the study. By the end of the 3-hour observation period, the study had been interrupted in 13 patients in the control group and in 7 patients in the CPAP group, usually because of arterial hypoxemia (Table IV). The comparison of treatment failure frequency data in the 2 groups revealed differences of borderline significance ($p = 0.068$) (Fig. 2). Three patients in each group were not mechanically ventilated despite failure of the assigned treatment. Two patients in each group were intubated after the study had been completed, 1 because of reinfarction and pulmonary edema, 2 because of irreversible cardiogenic shock and 1 during cardiopulmonary resuscitation. The differences in the hospital mortality and in the total frequency of ventilator treatment between groups were not statistically significant.

Discussion

Respiratory distress with associated hypertension and tachycardia is a major threat to the ischemic myocardium of a patient having acute cardiogenic pulmonary edema. Several theoretical aspects favor the use of CPAP as a primary method of providing respiratory support to these patients. The increase in transpulmonary pressure and functional residual capacity both reduces hypoxemia by decreasing intrapulmonary shunt and relieves respiratory work by improving lung compliance.

TABLE III Changes in Cardiopulmonary Variables During Three Hours of Breathing with an Ambient (Control [n = 7]) or Continuous Positive Airway Pressure (n = 13)

Time (min)		0	10	60	180
Respiratory rate (breaths/min)	Control	30 ± 6	28 ± 6	24 ± 5	20 ± 3*
	CPAP	30 ± 6	23 ± 5	22 ± 5	19 ± 5*
Pa_{O_2} (mm Hg)	Control	58 ± 6	58 ± 8	60 ± 7	65 ± 11
	CPAP	56 ± 8	63 ± 7	73 ± 12	84 ± 21*,†
Pa_{CO_2} (mm Hg)	Control	42 ± 13	39 ± 9	38 ± 7	37 ± 7
	CPAP	39 ± 9	37 ± 7	37 ± 6	38 ± 7
Arterial blood pH	Control	7.35 ± 0.14	7.38 ± 0.10	7.41 ± 0.07	7.43 ± 0.05‡
	CPAP	7.32 ± 0.07	7.34 ± 0.07	7.36 ± 0.08	7.37 ± 0.08*
Heart rate (beats/min)	Control	90 ± 16	93 ± 6	84 ± 10	92 ± 33
	CPAP	117 ± 25	107 ± 23	95 ± 20	93 ± 22*
Systolic arterial pressure (mm Hg)	Control	162 ± 25	153 ± 17	135 ± 21	137 ± 15*
	CPAP	140 ± 35	124 ± 26	119 ± 21	118 ± 22§
Diastolic arterial pressure (mm Hg)	Control	78 ± 10	77 ± 13	67 ± 10	70 ± 11‡
	CPAP	86 ± 20	77 ± 15	75 ± 11	73 ± 11§
Rate-pressure product/100 (mm Hg* × beats/min)	Control	144 ± 44	139 ± 19	113 ± 23	124 ± 46
	CPAP	163 ± 49	132 ± 36	113 ± 30	108 ± 29*

* $p < 0.001$ within 1 group; † $p < 0.05$ between the responses of the groups; ‡ $p < 0.05$ within 1 group; § $p < 0.01$ within 1 group.
All values are expressed as mean ± standard deviation.
CPAP = continuous positive airway pressure.

In the present study, 10 cm H_2O of CPAP applied with a face mask improved arterial blood oxygenation. A spontaneous improvement in gas exchange was very slow to occur in patients in the control group who breathed the same oxygen concentration with the same apparatus, but with an ambient airway pressure. A significant difference between the physiologic responses of the patients in the groups was evident throughout the study.

Several investigators mention a reduction of respiratory work as an advantage of CPAP therapy[3,5,6] although no definite proof of such an effect exists. Because we did not measure transpulmonary pressure change or tidal volume, we cannot directly assure that respiratory work decreased during either treatment. However, a decreased respiratory rate with subjectively determined less labored breathing, yet with a lower Pa_{CO_2} in the CPAP group is indirect objective evidence of decreased work of breathing.

Relief of respiratory distress was associated with significant cardiovascular effects in the patients who received CPAP. Arterial pressure, heart rate and rate-pressure product decreased significantly and persistently within 10 minutes, but existing hypotension was not aggravated. A similar but more gradual effect was noted during the 3-hour follow-up of patients in the control group as well. The hemodynamic response to CPAP indicates relief from the circulatory stress mediated by sympathoadrenergic drive in acute cardiogenic pulmonary edema.[11] The absence of adverse circulatory effects of CPAP is in accordance with findings in recent studies suggesting that elevated intrathoracic pressure does not impair the function of a failing left ventricle and in fact may assist it.[12–14] We started treatment and data collection in the acute phase of pulmonary edema when the patients were not yet instrumented for detailed hemodynamic assessment. Therefore, we cannot distinguish between the possible direct cardiovascular effects of CPAP and the indirect effects of improved pulmonary function, nor can we compare the relative importance of improved oxygenation and decreased respiratory work in relieving circulatory stress.

TABLE IV Causes of Failure of the Assigned Treatment*

	Control (n = 20)	CPAP (n = 20)
Failure criteria met before treatment	12	10
Failure during follow-up	13	7
Pa_{O_2} <50 mm Hg	9	4
Pa_{CO_2} >55 mm Hg	0	1
Respiratory rate >35 breaths/min	2	1
Cardiopulmonary resuscitation	1	1
Artificial airway required	1	0
Mechanically ventilated	12	6
Survived	14	17

* Differences not statistically significant.
CPAP = continuous positive airway pressure.

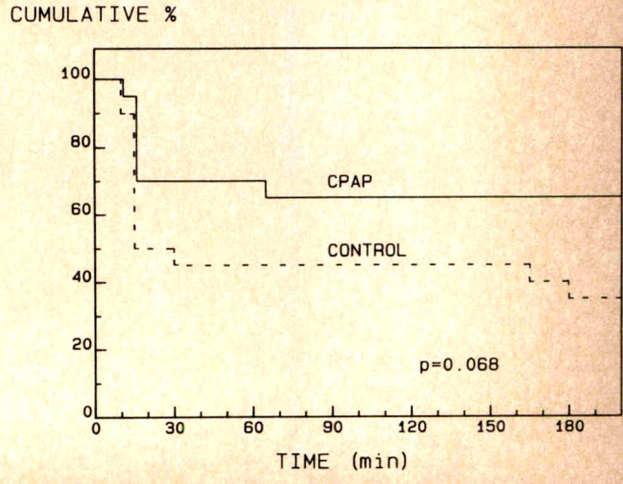

FIGURE 2. Cumulative percentage of patients remaining in the study during the 3-hour observation period. CPAP = continuous positive airway pressure.

The assigned therapy was not sufficient to prevent the need for mechanical ventilation in one-third of the patients who received CPAP, and in two-thirds of those who breathed with an ambient airway pressure ($p = 0.068$). A study involving more patients is required to confirm or refute the clinical significance of this trend and to determine whether early CPAP therapy has an effect on the outcome of patients who present with cardiogenic pulmonary edema. Some of the therapeutic failures may have been avoided in both groups by allowing adjustment of inspired oxygen and CPAP levels. Because the therapeutic effect of increased alveolar oxygen partial pressure depends on the magnitude of intrapulmonary shunt,[15–17] appropriate administration of CPAP can be expected to enhance the effect of supplemental oxygen particularly when the shunt is large. Thus, the elevation of inspired oxygen concentration in this study would have produced similar or even larger differences in gas exchange between the groups.

We conclude that 10 cm H_2O of continuous positive airway pressure administered by face mask improves gas exchange, decreases respiratory work, unloads circulatory stress, and may reduce the need for ventilator treatment in patients with acute cardiogenic pulmonary edema. Because of its safety, simplicity and reversibility, this technique bridges the gap between the oxygen mask and the ventilator.

Acknowledgment: We thank the physicians, the nursing staff and the laboratory personnel of the Emergency Department and the Intensive Care Unit at Helsinki University Central Hospital for their cooperation. We also are grateful to Markku Kupari, MD, for reviewing the manuscript and to Martha Gaber Abrahamsen for editing it for style.

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Intracoronary Thrombolytic Therapy in Acute Myocardial Infarction: A Prospective, Randomized, Controlled Trial

ALBERT E. RAIZNER, MD, FRANCISCO A. TORTOLEDO, MD, MARIO S. VERANI, MD, and RICHARD E. VAN REET, MD, *with* JAMES B. YOUNG, MD, FRANK D. RICKMAN, MD, W. RICHARD CASHION, MD, DAVID A. SAMUELS, MD, CRAIG M. PRATT, MD, MOHAMMED ATTAR, MD, HOWARD S. RUBIN, MD, JOHN M. LEWIS, MD, MILTON S. KLEIN, MD, and ROBERT ROBERTS, MD

A prospective, randomized trial was designed to assess the efficacy of intracoronary thrombolytic therapy with streptokinase (STK) in acute myocardial infarction. Sixty-four patients with acute myocardial infarction were randomized within 6 hours of onset of symptoms to 1 of 3 groups. Sixteen patients were treated by conventional means (control group). Nineteen patients underwent coronary arteriography and received corticosteroids and intracoronary and intravenous nitroglycerin (NTG group). Twenty-nine patients received management identical to that of the NTG group, with the addition of intracoronary STK therapy (STK group). Recanalization was demonstrated in 21 of 29 patients (72%) in the STK group. Global and regional ejection fraction (EF) was determined by radionuclide ventriculography before any intervention and 7 to 10 days later. No significant improvement in global EF was achieved in the control and NTG groups. In STK patients as a group, global EF did not increase significantly; however, in patients recanalized with STK, EF improved from 42 ± 17% to 49 ± 16% ($p = 0.023$). All groups showed wide variability of response. Improvement in global EF of more than 5% was noted in 44% of patients recanalized with STK. When subgrouped on the basis of initial global EF of 45% or less or more than 45%, only patients recanalized with STK with an initial EF of 45% or less had an improved global EF (from 30 ± 10% to 42 ± 10%, $p = 0.015$). Regional EF of all involved infarct regions was improved only in the STK group (from 34 ± 19% to 42 ± 23%, $p = 0.027$) and STK-recanalized subgroup (from 33 ± 18% to 45 ± 24%, $p = 0.003$). When only the most involved infarct regions were analyzed, control, NTG and STK groups improved, with patients recanalized with STK showing the greatest degree of improvement. Thus, this trial demonstrates a beneficial effect of thrombolytic therapy in global and, more strikingly, in regional function in patients in whom recanalization with STK is successful, with predominant benefit in those with initially depressed left ventricular function.

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Nonsurgical revascularization in acute myocardial infarction (AMI) has been achieved with intracoronary administration of streptokinase (STK),[1–10] and initial studies suggested that successful thrombolysis improves ventricular performance. More recently, prospective, randomized controlled studies have been published,[11–13] but conclusions regarding effects on left ventricular function conflict. Because most STK trial protocols include a variety of medications, such as corticosteroids, vasodilators and anticoagulants, which may themselves contribute to beneficial results, we felt that a group should be treated identically to the patients receiving STK except for the omission of STK. Accordingly, we performed such a study using a prospective, randomized trial design.

Methods

Patients admitted to The Methodist Hospital, Houston, with prolonged chest pain were considered for entry to the study if they met the following criteria: (1) chest discomfort suggestive of myocardial ischemia lasting more than 1 hour

From the Section of Cardiology, Baylor College of Medicine, and The Methodist Hospital, Houston, Texas. This study was supported by The Methodist Hospital, Houston, Texas. Manuscript received September 18, 1984; revised manuscript received November 1, 1984, accepted November 2, 1984.

Address for reprints: Albert E. Raizner, MD, Section of Cardiology, The Methodist Hospital, 6535 Fannin Street/MS F1000, Houston, Texas 77030.

TABLE I Clinical Characteristics of the Three Groups at Entry into the Study

	Control (n = 16)	Nitroglycerin (n = 19)	Streptokinase (n = 29)
Age (yr)*	57 ± 8	58 ± 10	54 ± 11
Sex			
Male	13 (81%)	15 (79%)	24 (83%)
Female	3 (19%)	4 (21%)	5 (17%)
Prior infarction	1 (6%)	1 (5%)	3 (10%)
Site of infarction			
Anterior	7 (44%)	9 (47%)	16 (55%)
Inferior	9 (56%)	10 (53%)	13 (45%)
Killip class on admission			
I–II	15 (94%)	18 (95%)	24 (83%)
III–IV	1 (6%)	1 (5%)	5 (17%)
Time (hours) from onset of chest pain*			
To entry	3.68 ± 2.02	3.41 ± 1.44	3.54 ± 1.74
To intervention	. . .	5.29 ± 1.36	5.62 ± 1.75

* Mean ± standard deviation.
All intergroup differences are not statistically significant ($p > 0.05$).

and not relieved by nitroglycerin (NTG); (2) electrocardiographic abnormalities compatible with AMI, consisting of ST-segment elevation or depression greater than 1 mV, or the development of new Q waves; and (3) onset of chest discomfort within 6 hours of arrival at the hospital. Myocardial infarction was confirmed by serial analysis of plasma MB-creatine kinase. Criteria for exclusion were: (1) cardiogenic shock; (2) 70 years of age or older; (3) presence of actively bleeding lesions; (4) severe hypertension (blood pressure greater than 200 mm Hg systolic or 120 mm Hg diastolic); (5) stroke within the preceding 2 weeks; (6) major surgery within the preceding 2 weeks; and (7) treatment with STK within 1 year or known hypersensitivity to STK. Patients meeting the entry criteria were informed of the nature of the study, and if they consented to participate, were randomized to 1 of 3 groups by a computer-generated random sequence.

Patients in group I (control group) received standard care in the coronary care unit as per usual practice. Coronary arteriography was not performed on admission in this group, but was done in most patients within 3 weeks. Anticoagulant drugs were not routinely administered to these patients.

Patients in groups II and III underwent right- and left-sided cardiac catheterization with coronary angiography by either the brachial or femoral artery approach under systemic anticoagulation with 5,000 units of heparin. Multiple projections were obtained of both coronary arteries and the vessel responsible for the infarction was identified. Patients in group II (NTG group) received intracoronary NTG, 0.2 to 0.4 mg, in the infarct-related artery followed by repeat coronary angiograms 3 to 5 minutes later. Patients in group III (STK group) received, in addition to intracoronary NTG as in group II, intracoronary STK given as a bolus of 20,000 IU in 2 to 3 minutes, followed by an infusion at the rate of 4,000 IU/min, which was continued until a dose of 250,000 IU was administered. Repeat arteriograms were obtained every 15 minutes. Both NTG and STK groups received 5 mg of Decadron® intravenously before coronary arteriography. Patients in both groups received intravenous NTG, 50 to 70 μg/min, for 24 hours under hemodynamic monitoring, followed by oral or topical nitrates. They also received dipyridamole, 75 mg orally 3 times/day; aspirin, 5 grains/day orally; and heparin, 5,000 IU subcutaneously every 8 hours until ambulating. Beta-blocking drugs and calcium channel-blocking drugs were avoided unless specifically indicated for arrhythmia or post-infarction angina.

Blood samples were obtained from all 3 groups on admission and every 6 hours for 48 hours for plasma MB-creatine kinase determination by electrophoresis. All 3 groups were given lidocaine, 100 mg i.v. bolus on admission, followed by continuous i.v. infusion of 2 to 4 mg/min for 48 hours.

To allow for the fact that not all STK (group III) patients would be successfully recanalized and to provide a sufficient number of patients in the STK group to analyze "recanalized" and "nonrecanalized" subgroups, 50% of patients were randomized to group III and only 25% each were randomized to groups I and II.

Radionuclide ventriculography: After intravenous injection of 20 mCi of technetium-99m for red cell labeling, radionuclide blood pool ventriculograms were obtained in the left anterior oblique projection with the best septal separation (usually 30 to 40°). The first study was obtained on admission, before cardiac catheterization, and the study was repeated 7 to 10 days later using the same gamma camera.

Global and regional left ventricular ejection fractions (EF) were determined using commercially available software (Technicare). Regional EFs were calculated using a modification of a previously reported technique.[14] The left ventricular silhouette was bisected from base to apex and divided into 3 equal segments of approximately 120° each: septal, inferoapical and posterolateral segments.

All of the radionuclide studies were processed and interpreted by 1 experienced observer without knowledge of the patients' group, clinical or angiographic result or whether the study was being performed before or after treatment. In our laboratory, the inter- and intraobserver correlation coefficients are, respectively: global EF, 0.97 and 0.95; septal EF, 0.82 and 0.86; inferoapical EF 0.97 and 0.97; and posterolateral EF, 0.97 and 0.88. The normal value in our laboratory for global left ventricular EF is 64 ± 6% and for regional EF as follows: septal, 66 ± 13%, inferoapical, 63 ± 7%; and posterolateral, 67 ± 9%.

Regional left ventricular function of the areas involved in the infarction were analyzed in 2 ways: *All involved regions*—anterior infarctions tended to involve more than 1 segment, whereas inferior infarctions typically involved only 1 segment. *Most involved region*—the 1 segment per patient with the lowest regional EF. In patients with anterior infarction, this was either the septal or inferoapical segment. In patients with inferior infarction, this was either the inferoapical or posterolateral segment.

Coronary arteriographic data: We categorized the pretreatment infarct-related arteries as completely obstructed or subtotally obstructed. Complete obstruction was defined as the total absence of anterograde flow across the obstructed

TABLE II Angiographic Findings and Angiographic Response to Intracoronary Intervention

	Control* (n = 11)	Nitroglycerin (n = 19)	Streptokinase (n = 29)
Extent of coronary disease†			
1 vessel	3 (27%)	6 (32%)	12 (41%)
2 vessels	3 (27%)	7 (36%)	5 (17%)
3 vessels	5 (46%)	6 (32%)	12 (41%)
Infarct-related vessel			
Completely occluded	...	13 (68%)	16 (55%)
Subtotal occluded	...	6 (32%)	13 (45%)
Collaterals to infarct-related artery	...	8 (42%)	11 (38%)
Improved flow with nitroglycerin	...	3 (16%)	4 (14%)
Recanalized after streptokinase		...	21 (72%)

* Data are from 11 patients in whom arteriography was performed within 3 months of infarction.
† Significant stenosis considered to be at least 50% luminal diameter narrowing.

segment. Subtotal obstruction was defined as the presence of any anterograde flow across the obstructed segment. In most instances of subtotal obstruction, the flow in the distal vessel was sluggish, delayed in clearing and incompletely filled the distal vessel. In some, however, distal flow and runoff were reasonably good initially; such patients were still treated according to their treatment group.

An infarct-related coronary artery was considered to be "recanalized" if anterograde distal flow and runoff were seen after intervention.

Statistical analysis: Comparison of parameters on admission and 7 to 10 days later was evaluated by means of a paired *t* test. Comparison of frequency distributions between groups was performed with Fisher's exact or chi-square tests. For intergroup comparisons, 1-way analysis of variance was used. Statistical significance was at the $p < 0.05$ level, and results are reported as mean ± standard deviation.

Results

Patient characteristics: Sixty-six patients met initial entry criteria and were randomized to a treatment group. Two patients were subsequently excluded for failure to evidence elevation of MB-creatine kinase. Of the remaining 64 patients, 16 were randomized to the control group, 19 to the NTG group and 29 to the STK group. The clinical characteristics of the 3 groups at entry into the study are shown in Table I. There were no statistically significant differences between groups.

Angiographic findings: The baseline angiographic findings and the results of intracoronary intervention in the NTG and STK groups are shown in Table II.

Overall, complete occlusion of the infarct-related vessel was observed in 60% of all patients in the NTG and STK groups combined. Of the 29 patients who received intracoronary STK, 16 initially had a complete obstruction. In 8 of these patients the completely occluded arteries opened unequivocally to allow anterograde flow after STK infusion. In the 13 patients with subtotal obstruction, it was more difficult to assess improvement in flow because some anterograde flow was present initially. However, 8 of these 13 showed a reduction in the severity of stenosis and an increase in rate of contrast runoff; 5 others manifested equivocal improvement. Thus, 21 patients (72%), consisting of 8 who had initially complete obstruction and 13 with subtotal obstruction, had distal flow in the infarct-related artery after STK infusion and were therefore, considered to be recanalized.

Clinical course: The hospital course and clinical outcome of the 3 groups of patients are shown in Table III. There were no statistically significant differences between groups.

In the entire series, 6 patients died, for an overall mortality rate of 9%. No patients in the control group died, 2 (11%) in the NTG group died and 4 (14%) in the STK group died. In 4 of these 6 patients, the infarct-related artery remained occluded after intervention. Of the 2 patients in the NTG group who died, 1 had an admission EF of 22%, and the other died despite an

TABLE III Hospital Course and Clinical Outcome

	Control (n = 16)	Nitroglycerin (n = 19)	Streptokinase (n = 29)
Type of infarction evolved			
Transmural	15 (94%)	15 (79%)	23 (79%)
Subendocardial	1 (6%)	4 (21%)	6 (21%)
Ventricular arrhythmia	1 (6%)	1 (5%)	4 (14%)
Reperfusion arrhythmia	...	...	3 (10%)
Bleeding complications	0	0	2 (7%)
Postinfarction angina	3 (19%)	6 (32%)	9 (31%)
Early bypass surgery or angioplasty	1 (6%)	4 (21%)	5 (17%)
Extension or reinfarction			
<2 weeks	1 (6%)	1 (5%)	3 (10%)
2–6 weeks	0	0	2 (7%)
Deaths	0	2 (11%)	4 (14%)

All intergroup differences are not statistically significant ($p > 0.05$).

TABLE IV Global and Regional Ejection Fraction

		Global Ejection Fraction			Regional Ejection Fraction							
					All Involved Segments				Most Involved Segments			
Group or Subgroup	n*	Early	Late	p Value	n†	Early	Late	p Value	n†	Early	Late	p Value
Control, all	16	48 ± 12	50 ± 11	NS	22	34 ± 21	38 ± 17	NS	16	31 ± 19	39 ± 17	0.035
EF ≤ 45	8	37 ± 5	41 ± 8	NS	...	...	...	...	...	...	...	...
EF > 45	8	58 ± 4	59 ± 4	NS	...	...	...	...	...	...	...	...
Nitroglycerin, all	16	54 ± 11	57 ± 11	NS	22	47 ± 19	53 ± 19	NS	16	42 ± 17	52 ± 19	0.022
EF ≤ 45	4	42 ± 1	45 ± 8	NS	...	...	...	...	...	...	...	...
EF > 45	12	59 ± 9	61 ± 8	NS	...	...	...	...	...	...	...	...
Streptokinase, all	22	43 ± 17	46 ± 16	NS	34	34 ± 19	42 ± 23	0.027	22	32 ± 19	43 ± 26	0.011
EF ≤ 45	12	30 ± 7	38 ± 15	NS	...	...	...	...	...	...	...	...
EF > 45	10	59 ± 8	57 ± 6	NS	...	...	...	...	...	...	...	...
Recanalized	16	42 ± 17	49 ± 16	0.023	25	33 ± 18	45 ± 24	0.003	16	30 ± 17	48 ± 27	0.003
EF ≤ 45	9	30 ± 10	42 ± 10	0.015	...	...	...	...	...	...	...	...
EF > 45	7	58 ± 7	59 ± 5	NS	...	...	...	...	...	...	...	...
Nonrecanalized	6	45 ± 19	39 ± 16	NS	9	37 ± 24	32 ± 18	NS	6	32 ± 25	31 ± 23	NS

* Number of patients.
† Number of regions.
Numbers shown for ejection fraction are percentages (mean ± standard deviation).
NS = not statistically significant ($p > 0.05$).

initial EF of 49% when severe hypotension developed after intracoronary NTG treatment. In the STK group, 3 of the 4 patients who died had extremely low admission EFs (12%, 19% and 23%). None of these patients had successful recanalization with STK. One patient with an admission EF of 57% died after coronary artery bypass surgery, performed because of continued ischemic episodes. This was the only death among STK-recanalized patients.

Assessment of left ventricular function: Radionuclide ventriculograms done on admission, before any intervention (early study) and at 7 to 10 days after infarction (late study) were available in 16 (100%) of the control patients, 16 (84%) of NTG patients and 22 (76%)

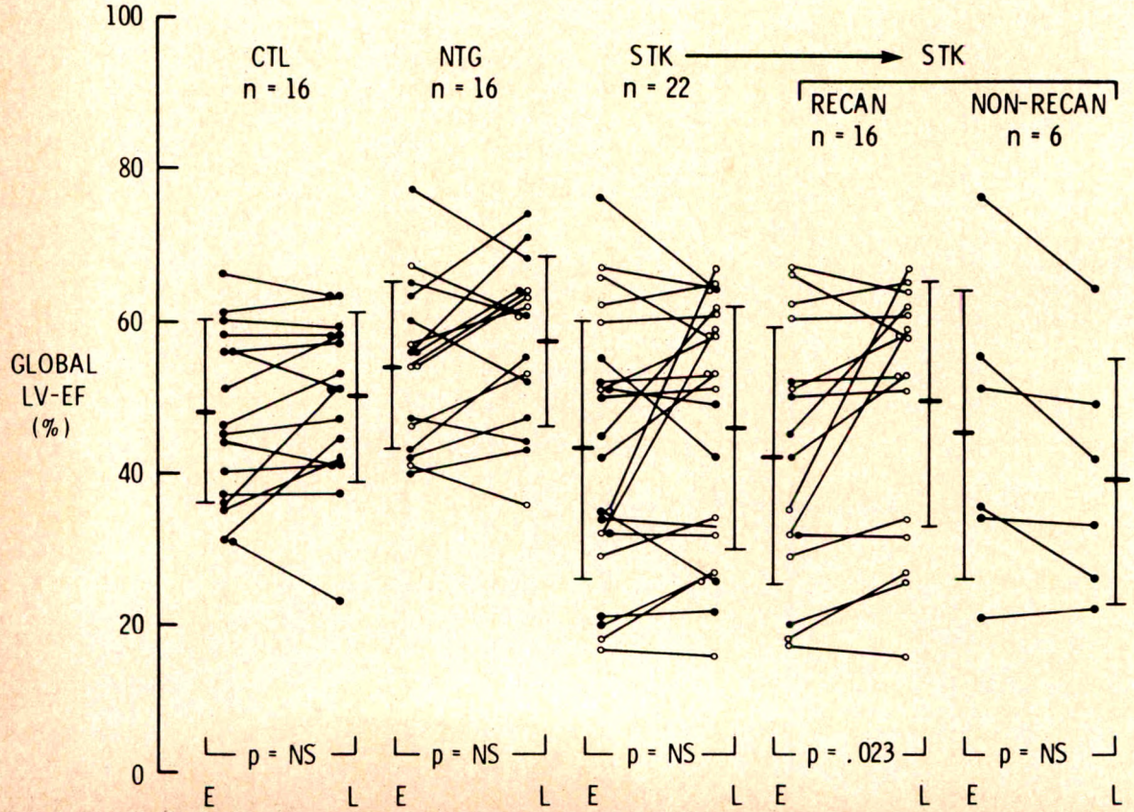

FIGURE 1. Global left ventricular ejection fraction (LV-EF) early (E) (before intervention) and late (L) (7 to 10 days) in the 3 study groups: Control (CTL), nitroglycerin (NTG) and streptokinase (STK). The STK group is separated into recanalized (RECAN) and nonrecanalized (NON-RECAN) subgroups. In the NTG and STK groups, **closed circles** indicate a completely occluded artery and **open circles** incomplete occlusion or recanalization.

of the STK patients. These data are shown in Table IV and individual measurements are shown in Figures 1 to 4.

The initial EF was somewhat lower in the STK group, but differences between the groups were not statistically significant. There were no statistically significant changes in left ventricular global EF from early to late study in either of the 3 groups. Much variability of response was seen within each group; global EF increased impressively in some patients and decreased in others (Fig. 1). When the patients in the STK group were separated into recanalized and nonrecanalized subgroups, global left ventricular EF increased significantly (from 42 ± 17% to 49 ± 16%, p = 0.023) in patients with recanalized vessels. An opposite trend was observed in those patients whose infarct-related vessel remained occluded (from 45 ± 19% to 39 ± 16%), but this latter change narrowly failed to achieve statistical significance (p = 0.06).

When the STK-recanalized group was further subdivided based on an early EF of 45% or less or more than 45%, the global EF significantly improved in patients whose initial EF was 45% or less, but showed no significant change in patients whose initial EF was more than 45% (Fig. 2). The prevalence of anterior infarction was higher in the subgroup with initially depressed EF (8 of 9) while inferior infarction predominated in those with normal EF (6 of 7) (p <0.01). There were no significant differences between early and late global EF in the control and NTG groups when similarly subdivided according to initial EF (Fig. 2).

Subdividing the STK-recanalized patients into those whose infarct-related artery was incompletely occluded (subtotal) before treatment and those with initially complete occlusion revealed a comparable magnitude of improvement in global EF in both subgroups. Global EF in the former subgroup increased from 44 ± 20% to 51 ± 18% (p = 0.1, n = 10) and in the latter subgroup from 40 ± 12% to 46 ± 18% (p = 0.08, n = 6). Similar subdivision of the NTG group showed no greater improvement in global EF among those with incomplete occlusion before treatment (from 53 ± 9% to 57 ± 11%, p = 0.3, n = 6) compared to those with complete occlusion (from 55 ± 12% to 58 ± 11%, p = 0.3, n = 10).

Regional left ventricular ejection fraction: Data on regional left ventricular function of the areas involved in the infarction are shown in Table IV.

All involved segments: There was much variability of response in all groups (Fig. 3). Some patients in each group showed large increases and other decreases in regional EF. A statistically significant improvement in the mean regional EF was observed only in the STK group (from 34 ± 19% to 42 ± 23%, p = 0.027). No statistically significant change in regional function was observed in the control or NTG groups. Additionally, in the STK-recanalized patients EF improved more markedly from 33 ± 18% to 45 ± 24% (p = 0.003). In contrast, nonrecanalized patients tended to have de-

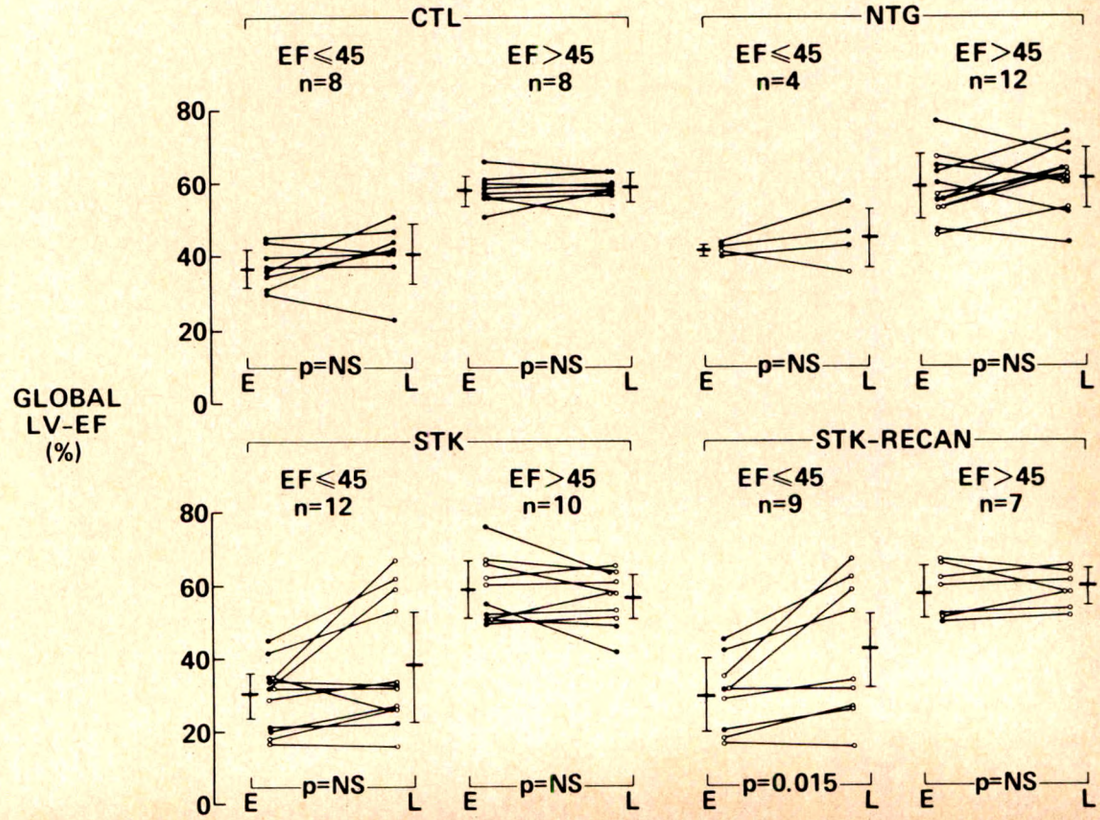

FIGURE 2. Global left ventricular ejection fraction (LV-EF) in the study groups, subdivided according to EF on admission. Abbreviations and symbols as in Figure 1.

terioration in regional EF (from 37 ± 24% to 32 ± 18%), although this change was not statistically significant.

Most involved segments: When only the infarct segments whose EF was most depressed were analyzed, statistically significant improvement in regional EF was observed in the control, NTG, STK and STK-recanalized groups (Fig. 4, Table IV). The greatest magnitude of improvement, however, occurred in the STK-recanalized patients, whose infarct-region EF increased from 30 ± 17% to 48 ± 27% ($p = 0.003$).

Discussion

Our study addresses the hypothesis that nonsurgical coronary artery recanalization in patients with AMI improves left ventricular function. With this aim, we designed a prospective, controlled study in which patients were randomized to 1 of 3 groups. This study design is unique relative to previously reported randomized trials in using 2 control groups, including a group (NTG) managed identically to the treatment group (STK) except for STK therapy. The primary endpoint in this short-term study was left ventricular function as measured by global and regional EF. The results of this study support the hypothesis that recanalization with thrombolytic therapy results in improved left ventricular function following AMI with improved function occurring in the segments involved with infarction. Additionally, the greatest benefit appears to be in those patients with more serious indication of initial myocardial dysfunction. Lack of improvement or deterioration in global EF was noted in those in whom the infarct vessel remained occluded. A similar observation was made by Timmis et al.[7]

The conclusion that thrombolytic therapy improves global left ventricular function needs qualification. The benefits in left ventricular function observed in the STK-recanalized subgroup is not seen in all patients within this subgroup (Fig. 1 and 2). In fact, in only 7 of 16 patients (44%) in this subgroup did global EF improve by 5% or more, and in only 4 of 16 (25%) did it improve by 10% or more. These few patients who benefited form the basis for the subgroup's mean improvement. Improvement in global EF of 5% or more was observed in 5 of 16 control patients (31%) and 7 of 16 NTG patients (44%). These latter groups, as with the STK group, manifested much individual variability, offsetting the gains in global EF in some.

Analysis of regional EF further substantiates the benefits of successful recanalization. When all infarct-involved segments are analyzed, only the STK and STK-recanalized patients manifest statistically significant improvement. Again, variability among patients within each group is prominent. When only the most involved (most depressed) segment for each patient is tabulated, significant improvement in regional EF is observed for the control, NTG and STK groups, and

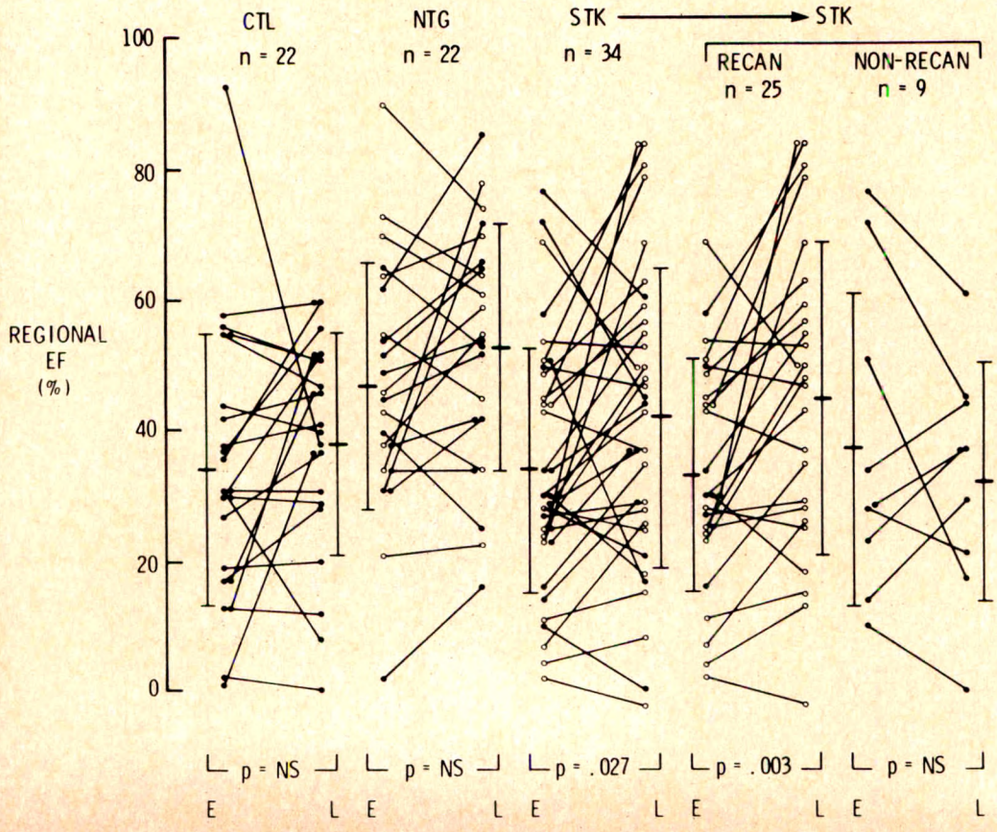

FIGURE 3. Regional ejection fraction (EF) of all involved regions. Early (E) (before intervention) and late (L) (7 to 10 days) in the study groups. Abbreviations and symbols as in Figure 1.

STK-recanalized subgroup. This observation would support the concept of "stunned" but viable myocardial tissue within the infarct region, capable of regaining function with time.[15] The magnitude of regional improvement was greatest in STK-recanalized patients. Improvement in regional function, however, does not directly translate into improved global function. Global EF may not change if noninvolved regions initially hypercontract and gradually return to normal as infarct-involved regions improve.[16] Consequently, regional EF may be a more sensitive measure of a beneficial effect of thrombolytic therapy, and appropriately so, because AMI is primarily a segmental disease. The apparently conflicting results of the randomized studies by Anderson et al,[11] Khaja et al[12] and the Western Washington trial[13] may be explained by the failure to examine early and late regional function in these studies.

Of major importance is the observation that the greatest improvement in left ventricular global and regional function was observed among patients whose EF was substantially reduced (≤45%) on admission. In those patients, EF increased from 30 ± 10% to 42 ± 10% ($p = 0.015$) when recanalization was achieved. These are the patients who would probably benefit with an aggressive intervention. Overwhelmingly, this group was composed of patients with anterior infarction. Thus, we have identified a subgroup of patients, those with initially depressed left ventricular function and, in particular, anterior infarction with depressed left ventricular function, in whom intracoronary thrombolytic therapy appears to be most efficacious. The clinical implication of this latter observation is important. Were intracoronary thrombolytic therapy to be used on a routine basis, the cost in terms of medical manpower, hospital manpower, facility utilization and public cost would be enormous. Applying this procedure to those who appear to benefit most may be a reasonable goal.

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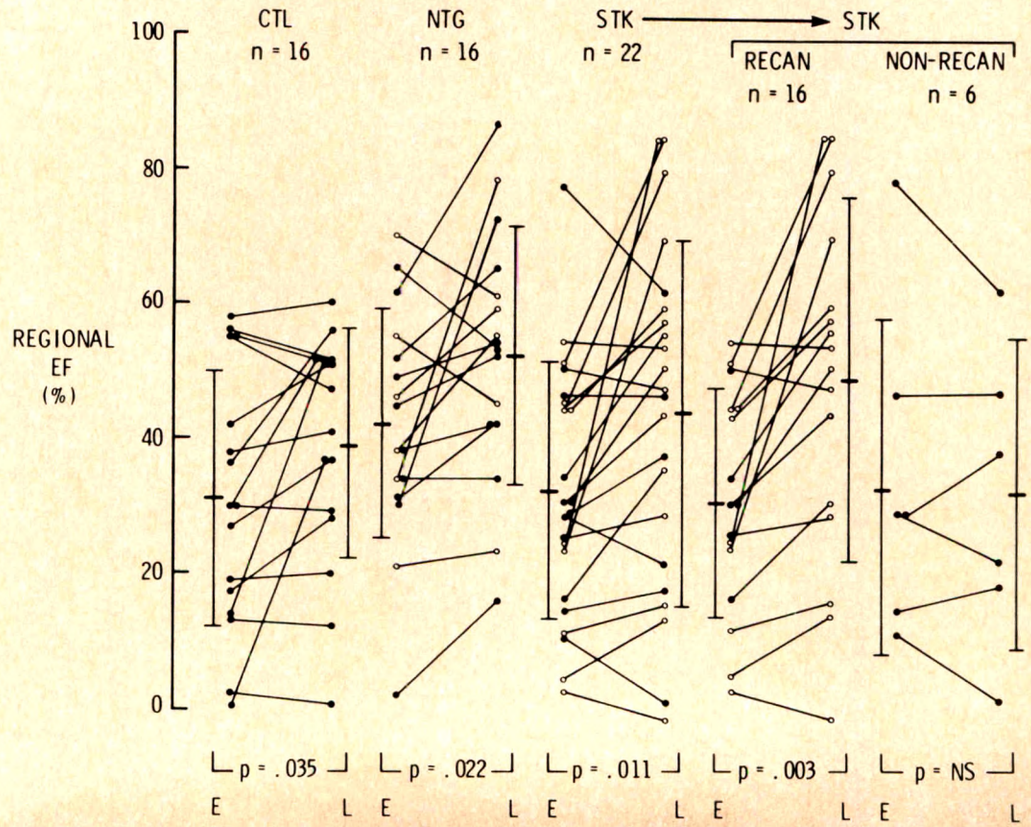

FIGURE 4. Regional ejection fraction (EF) for most involved infarct regions (1 per patient) early (E) (before intervention) and late (L) (7 to 10 days) in the study groups. Abbreviations and symbols as in Figure 1.

ciated. Streptokinase used in this study was provided by Pharmacia. Computational assistance was provided by The CLINFO Project, funded by grant RR-00350, Division of Research Resources, National Institutes of Health.

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Intravenous Versus Intracoronary Streptokinase in Acute Myocardial Infarction

RUSSELL P. VALENTINE, MD, DOUGLAS E. PITTS, MD,
JO ANN BROOKS-BRUNN, RN, MSN, JAMES G. WILLIAMS, MS,
EUGENE VAN HOVE, MD, and PAUL E. SCHMIDT, MD

One hundred sixty-four consecutive patients with acute myocardial infarction were enrolled in a prospective trial of coronary thrombolysis with streptokinase (STK). The first 98 patients received intracoronary (i.c.) STK after coronary angiography and the next 66 received a high-dose rapid infusion of STK (900,000 IU) intravenously (i.v.) before angiography. First-pass radionuclide ejection fraction (EF) was performed early (within 24 hours of admission) and late (10 to 14 days after admission) to evaluate left ventricular function. In the i.v. group, 42 of 66 (64%) of infarct-related arteries were patent at the initial angiogram and 6 (9%) opened with subsequent i.c. STK. In the i.c. group, 13 of 98 (13%) of infarct-related arteries were patent at the initial angiogram and 50 of 85 (59%) opened with the i.c. STK. The i.v. and i.c. groups did not differ in time from onset of chest pain to presentation, type of infarct or underlying severity of coronary artery disease. In the i.v. group, STK was begun 67 minutes earlier than in the i.c. group. In 62 patients in whom reperfusion was successful, mean EF increased from 39 ± 11% early to 48 ± 13% late. In 30 in whom it was not, the mean EF increased from 36 ± 10% to 40 ± 12%. The increase in EF was significantly greater in patients in the reperfused group ($p < 0.03$). In 18 patients who underwent reperfusion by i.v. STK, the mean EF increased 11 ± 12%, whereas in 44 patients who had reperfusion by i.c. STK, the mean EF increased 9 ± 10% (difference not significant). Complications of the lysis procedure were similar in the i.v. and i.c. groups. Thus, i.v. and i.c. STK are of comparable efficacy and safety in establishing reperfusion of the infarct-related artery in patients with acute myocardial infarction.

(Am J Cardiol 1985;55:309–312)

Thrombosis of a coronary artery usually underlies acute myocardial infarction (AMI),[1] and the thrombus can be lysed with regional administration of streptokinase (STK) in most patients.[2–4] There is also evidence that reperfusion improves left ventricular function[5–7] and reduces the mortality rate from AMI.[8] Nevertheless, the intracoronary (i.c.) administration of STK is impractical because of limited access to the facilities and personnel necessary for its use. Intravenous (i.v.) STK does not require specialized facilities and can be performed earlier in the course of AMI. If the efficacy and safety of i.v. STK are comparable to i.c. STK, then its wider applicability and potential for earlier administration could have substantial impact on the treatment of patients with AMI.

We studied 164 consecutive patients in a nonrandomized prospective trial of coronary thrombolysis in patients with AMI. The first 98 patients were treated with i.c. STK (i.c. patients), and the subsequent 66 patients with i.v. STK (i.v. patients). In this report we compare the efficacy and safety of these 2 treatment methods.

Methods

Patients: We prospectively evaluated 191 patients with AMI who presented to the hospital within 6 hours of the onset of chest pain from October 1981 to March 1984. AMI was diagnosed by unequivocal ST-segment elevation, which did

From the Cardiovascular Section and Department of Medical Research, Methodist Hospital of Indiana, Inc., Indianapolis, Indiana. Manuscript received May 7, 1984; revised manuscript received September 9, 1984, accepted September 25, 1984.

Address for reprints: Russell P. Valentine, MD, Department of Medical Research, Methodist Hospital of Indiana, Inc., 1604 North Capitol Avenue, Indianapolis, Indiana 46206.

TABLE I Frequency of Reperfusion

Group	No. of Pts	Patent at Initial Angiogram (%)	Patent After i.c. Infusion (%)
i.c.	98	13	64
i.v.	66	64	74

i.c. = intracoronary; i.v. = intravenous.

not revert with the administration of nitrates. Patients were excluded for: (1) age over 80 years, (2) active gastrointestinal bleeding within 6 months, (3) cerebrovascular accident within 2 years, (4) surgery within 2 weeks, (5) recent external cardiac massage, and (6) absence of valid consent form. One hundred sixty-four patients who gave informed consent (approved by the Institutional Review Board) were included in this analysis. One hundred thirty-one were men. The average age of the patients was 57.1 ± 9.2 years (range 36 to 78).

Study protocol: *Intracoronary group:* Patients received i.v. heparin, 5,000 U, and an i.v. bolus of lidocaine hydrochloride, 1.0 to 1.5 mg/kg body weight, followed by a continuous infusion of 2 to 4 mg/min. Coronary angiograms were performed using the Seldinger technique and Judkins catheters through a percutaneous sheath. If occlusion of the infarct-related artery persisted after 400 μg of i.c. nitroglycerin, 20,000 IU of STK (Kabikinase®) was administered as a bolus followed by an infusion at 4,000 U/min. Angiography of the vessel was repeated every 15 minutes. The infusion was continued 30 minutes after lysis or until 2 consecutive angiograms showed no change in the amount of i.c. clot. If patency did not occur, the infusion was discontinued after 60 minutes. Left ventriculography was performed after the STK infusion. The average total dose of STK for i.c. patients was 213,000 ± 82,000 IU.

Intravenous group: The patients received 250 mg of i.v. hydrocortisone, an infusion of i.v. lidocaine (see i.c. group) and then 900,000 IU of STK. Cardiac catheterization was then performed, and i.c. STK administered (per i.c. group protocol) if the infarct-related artery was occluded at the time of initial angiography or if significant flow-restricting coronary thrombosis remained. The average total dose of STK for i.v. patients was 993,000 ± 182,000 IU.

After successful lysis, partial thromboplastin time was measured serially, and continuous i.v. heparin was administered to maintain partial thromboplastin time at 2 to 2½ times the control for at least the first 72 hours after the procedure. Aspirin (5 grains twice daily) and dipyridamole (25 mg 3 times daily) were administered orally. The percutaneous sheath was removed 24 to 72 hours after the procedure while the heparin infusion was interrupted briefly. All study patients had documentation of their clinical course, including the incidence of complications. Each patient underwent clinical reevaluation at 2, 6 and 12-month follow-up intervals. First-pass radionuclide ventriculography was performed within 24 hours of admission, at discharge and at the follow-up intervals using technetium-99m-DTPA and a multicrystal camera. Patients who underwent coronary artery bypass grafting before their follow-up nuclear studies were excluded from analysis of ventricular function. Also, patients without total occlusion of the infarct-related artery were not included in this analysis.

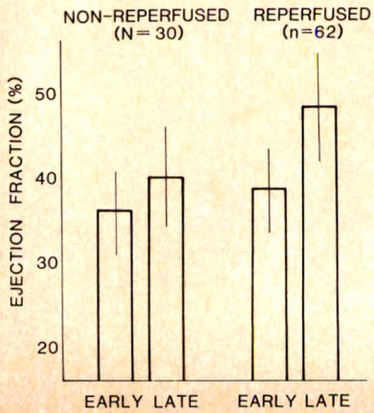

FIGURE 1. Effect of lysis on left ventricular function. Ejection fraction changes from admission (early = within the first 24 hours) to time of discharge (late = 10 to 14 days after admission) in reperfused and nonreperfused patients.

Data analysis: The patency rate of the infarct-related vessel on the initial angiogram and the time from onset of pain to initial administration of the STK were compared in the i.v. and i.c. groups. Comparison of left ventricular ejection fraction (EF) was made between patients who did and did not have successful lysis. Chi-square analysis was used to make these comparisons.

Results

Frequency of reperfusion (Table I): The i.v. and i.c. groups did not differ with respect to time from onset of chest pain to presentation, onset of chest pain to beginning of cardiac catheterization, demographic data or overall severity of coronary artery disease. Of 98 patients in the i.c. group, 13 (13%) had a patent infarct-related artery on initial angiography. Reperfusion occurred in 50 of the 85 (59%) who received i.c. STK. A total of 63 of 99 (64%) had a patent infarct-related artery at the conclusion of the procedure.

Of 66 patients in the i.v. group, 42 (64%) had a patent infarct-related artery on initial angiogram. Reperfusion occurred in an additional 6 patients after receiving i.c. STK for a total patency rate of 48 of 66 (74%). If the 13% incidence of spontaneous patency seen in the i.c. group applies to the i.v. group, then i.v. STK achieved lysis in 51% of patients.

Time to treatment: The mean time from the onset of chest pain to the administration of STK in the i.c. group was 241 ± 72 minutes, and in the i.v. group 174 ± 97 minutes. Therefore, lytic therapy was begun 67 minutes sooner using the i.v. route.

Effect on left ventricular function (Fig. 1): Early (24 hours) and late (10 to 14 days) radionuclide EF data are available in 30 patients in whom reperfusion was not achieved and in 62 in whom it was achieved. In nonreperfused patients, the mean early EF was 36 ± 10%, the mean late EF was 40 ± 12% and the mean increase was 3.8 ± 9.8%. In reperfused patients, the mean early EF was 39 ± 11%, the mean late EF was 48 ± 13% and the mean increase was 9.5 ± 10%. The increase in EF was significantly greater in the reperfused than in the nonreperfused group ($p < 0.03$). The groups did not differ in age, gender, risk factor prevalence or severity of coronary disease. Of the 62 reperfused patients in whom EF data are available, 44 were reperfused by the i.c. route and 18 by the i.v. route. The mean EF increase in i.c. patients was 8.7 ± 9.7% and in i.v. patients 11 ± 12%. These values do not differ significantly.

Complications (Table II): Sustained ventricular tachycardia, nonsustained ventricular tachycardia, or ventricular fibrillation occurred in 23 of 98 i.c. patients

(23%) and 17 of 66 i.v. patients (26%). Bleeding of sufficient magnitude to necessitate transfusion occurred in 5 of 98 i.c. patients (5%) and 2 of 66 i.v. patients (3%). Bleeding was invariably related to the catheterization site and occurred at least 24 hours after the catheterization procedure while patients were receiving heparin, aspirin and dipyridamole. One i.c. patient required direct surgical repair of the femoral artery. Apparent hypersensitivity reaction to STK (hives or other transient erythematous skin eruptions) occurred in 2 i.c. patients (2%) and 2 i.v. patients (3%). In 1 i.c. patient, transient renal failure accompanied a skin rash and an allergic interstitial nephritis was postulated. Hypotension temporally related to STK infusion occurred in 9 i.c. patients (9%) and 11 i.v. patients (17%). Mortality for the entire group was 9.6% and did not differ between lysed and nonlysed or between i.v. and i.c. groups.

TABLE II Complications

Complication	Group	
	i.c. (%)	i.v. (%)
Arrhythmia	23	26
Bleeding requiring transfusion	5	3
Arterial repair	1	0
Rash	2	3
Hypotension	9	17

Abbreviations as in Table I.

Discussion

Intravenous vs intracoronary streptokinase: Our results show that i.v. and i.c. STK are of comparable efficacy in patients with AMI. The incidence of patency of the infarct artery in patients who received i.v. STK was identical to that seen in those given i.c. STK (64%). In 98 patients given i.c. STK studied with coronary angiography, the frequency of spontaneous patency of the infarct-related artery was 13%. This incidence of spontaneous patency is in keeping with the study of DeWood et al[1] who found 10 to 13% of infarct arteries patent within the first 6 hours of infarction. When the i.c. group is used as a historical control group for the i.v. patients and a 13% spontaneous patency rate is assumed, the reperfusion rate attributable to the i.v. STK infusion is 51%, a value not significantly different from the 59% reperfusion rate achieved with i.c. STK. The lysis rates in the 2 groups may be similar because the lysis rate in the i.c. group is lower than in other studies. No apparent reason exists for this seemingly lower efficacy in our i.c. group, because patient selection criteria and treatment methods are similar to those of other studies. The 59% lysis rate seen in our study is not significantly different from the 60% lysis rate in the study of Khaja et al.[9]

The subsequent infusion of i.c. STK in patients who have received i.v. STK, but in whom the infarct artery is still occluded at the time of the initial angiogram, resulted in reperfusion in an additional 6 patients (9%) and a total patency rate of 74%. Whether this additional reperfusion is attributable to the i.c. infusion or to a delayed effect of the i.v. STK is difficult to determine. The latter is a possibility because high-dose systemic STK infusions may deplete all available plasminogen.[10] If this is the case, then i.c. STK infusion after a high-dose systemic STK infusion would be unlikely to have an additional effect. Therefore, the reperfusion rate of 51% with i.v. STK may represent a "minimum" efficacy. The actual rate of reperfusion may be higher if reperfusion achieved after the time of the initial angiogram was really a delayed effect of the i.v. infusion.

The i.v. group did have a significantly shorter interval of pain onset to institution of STK (175 ± 97 minutes) than the i.c. group (241 ± 72 minutes). The interval of pain onset to cardiac catheterization was the same in the 2 groups. Our protocol prevented us from determining the actual time of lysis in the i.v. group. It is tempting to use various clinical changes such as resolution of chest pain, return of ST segments to baseline and reperfusion ectopy to determine time of lysis. Various combinations of these findings were observed in our patients but were not consistently or predictably related to finding a patent artery at cardiac catheterization. No attempt was made to derive a time of lysis for the i.v. group. Nevertheless, because lysis occurred before catheterization in most patients in the i.v. group, lysis probably occurred sooner in i.v. than in i.c. patients.

The safety of i.v. STK was equivalent to that of i.c. STK. The incidence of bleeding complications was the same for each group, even though the i.v. group received a much higher total dosage of STK than the i.c. group. In both groups, bleeding complications occurred beyond 24 hours after conclusion of the catheterization procedure, presumably after STK effects had subsided and while patients were receiving heparin, aspirin and dipyridamole. There appears to be no hazard to percutaneous femoral artery puncture performed after high-dose systemic STK infusion. Hypersensitivity reactions were seen with equal frequency in each group. Transient hypotension temporally related to the STK infusion occurred in 9% of i.c. patients and in 17% of i.v. patients. This difference may be because i.v. patients received their infusions in much closer proximity to receiving nitrates (see Methods), but a dose or rate of administration response to STK cannot be discounted.

Changes in left ventricular function: Patients who underwent reperfusion of their infarct-related artery had an increase in radionuclide EF from admission to time of discharge of 9.5% (from 38.5 to 48.0%). This represents a 25% increase in EF from the admission value. Patients in whom reperfusion was not achieved had an increase in EF of 3.8% (from 36.1 to 39.9%), or an 11% increase from the admission value. The increase in EF seen in reperfused patients is significantly greater than that seen in nonreperfused patients ($p < 0.03$). These results differ from those of 2 earlier studies[9,11] in which radionuclide EF failed to improve after reperfusion. However, in these studies the initial EF was normal and an increase might not be expected to occur. There is agreement with the study of Smalling et al,[6] which showed a similar extent of improvement in EF in reperfused patients. Improvement in EF is seen in both i.v. and i.c. lysis groups (11% with i.v. and 8.7% with i.c., difference not significant).

Study limitations: It is beyond the scope of this study to discuss the issue of randomization of treatment

methods for which previous studies already yielded encouraging results. We elected not to randomize treatment in our trial and must acknowledge that the applicability of our findings is thereby limited. In this study, the test groups were studied sequentially and not concurrently, reflecting the sequential appearance of successful pilot studies, first of i.c. and then of i.v. STK. Therefore, no true control groups exist. Nevertheless, we believe that because selection criteria were identical and demographic data similar for the 2 test groups, valid comparisons of the treatment methods can be made.

As with most studies, the adequacy of the sample size is of concern. Although it can be determined that the lysis rates in the i.v. and i.c. groups do not differ, a type 2 error cannot be excluded; to do so would require a study of over 1,600 patients. This statistical confirmation therefore awaits much larger, multicenter trials.

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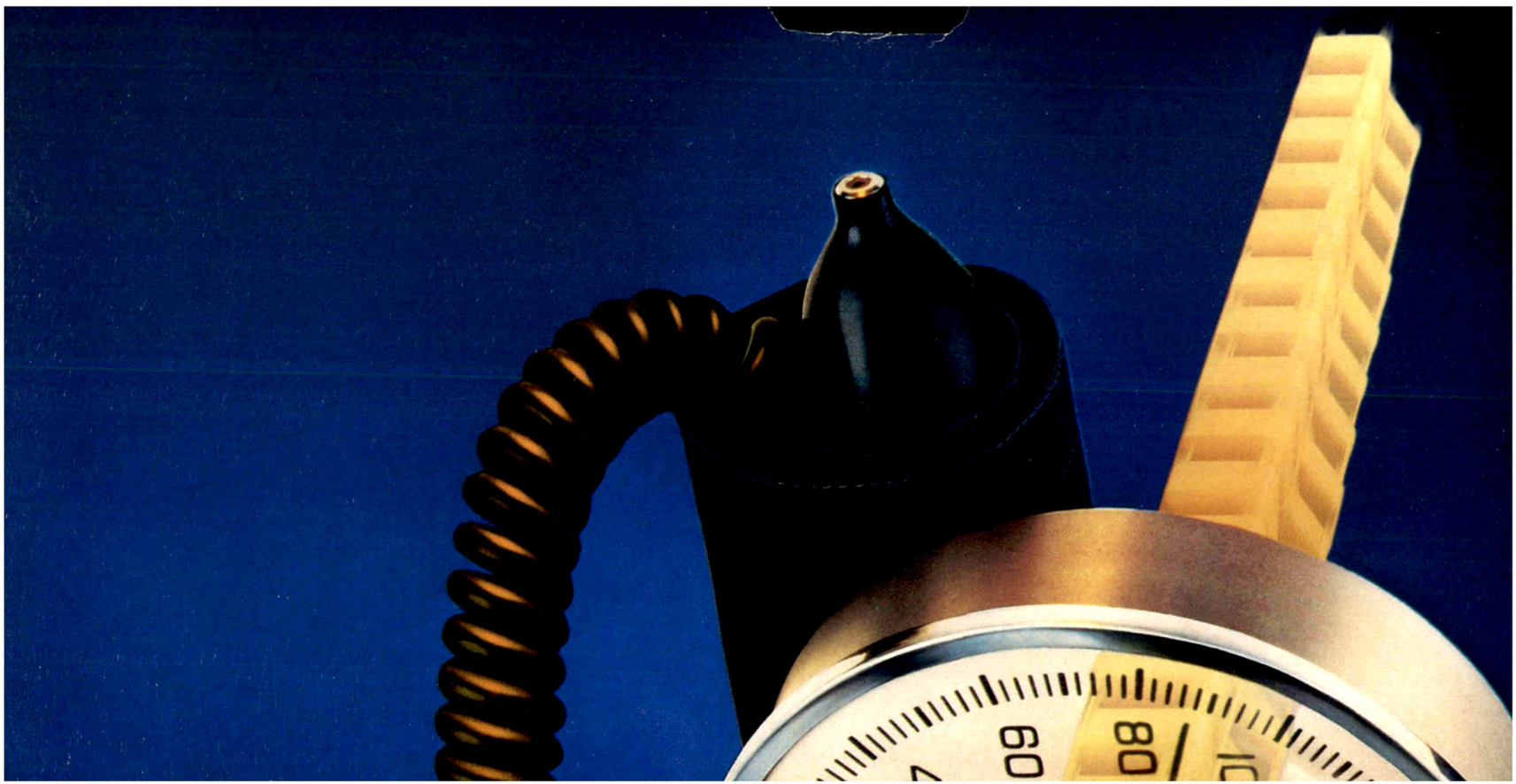

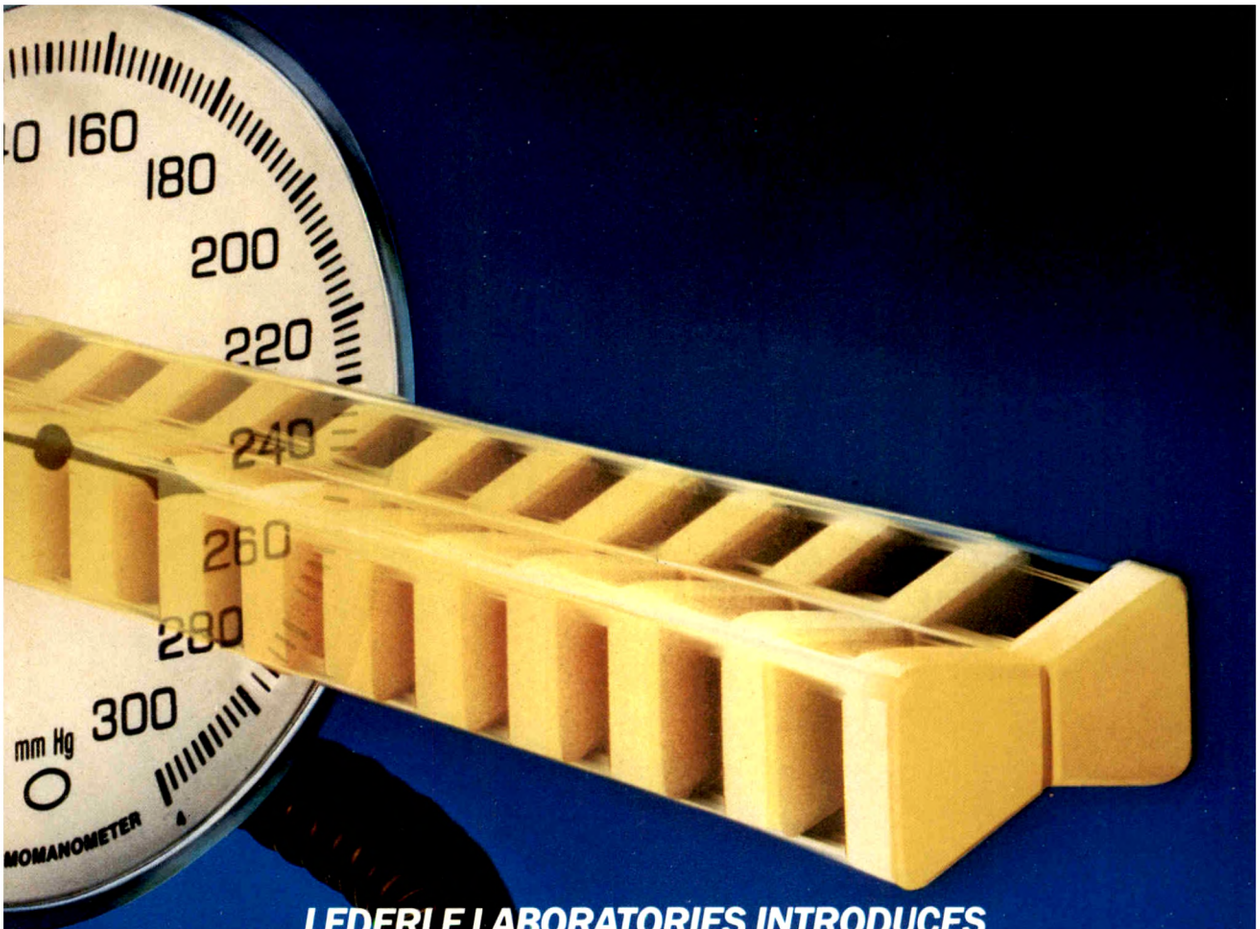

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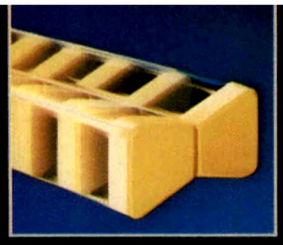
- **FOR PATIENTS TRANSFERRED FROM DYAZIDE®***

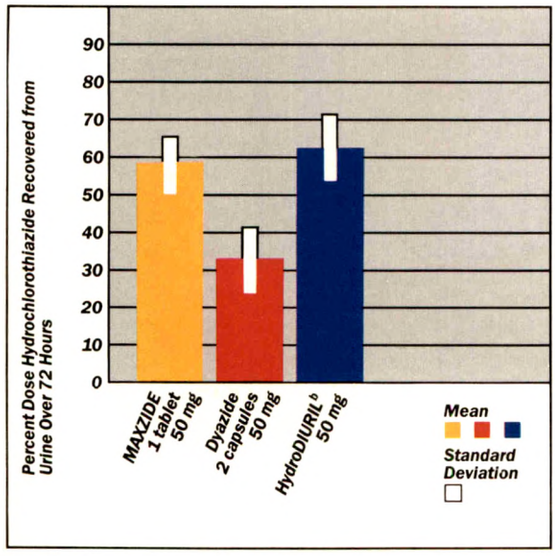
For the first time, a reliable alternative to the Dyazide formulation of triamterene hydrochlorothiazide — new MAXZIDE. In a transfer safety study, patients taking up to four Dyazide capsules daily were effectively transferred to MAXZIDE q.d. with no compromise in clinical condition.[1]



SUPERIOR DRUG DELIVERY AND ABSORPTION — TABLET TO TABLET, PATIENT TO PATIENT

MAXZIDE is optimally bioavailable and consistently delivers the prescribed dose of 75 mg triamterene and 50 mg hydrochlorothiazide. Dyazide, on the other hand, exhibits poor bioavailability. When given in equivalent doses, Dyazide delivers approximately half the amount of hydrochlorothiazide as MAXZIDE. Similarly, two Dyazide capsules deliver less than half the amount of triamterene as one MAXZIDE tablet.[2]

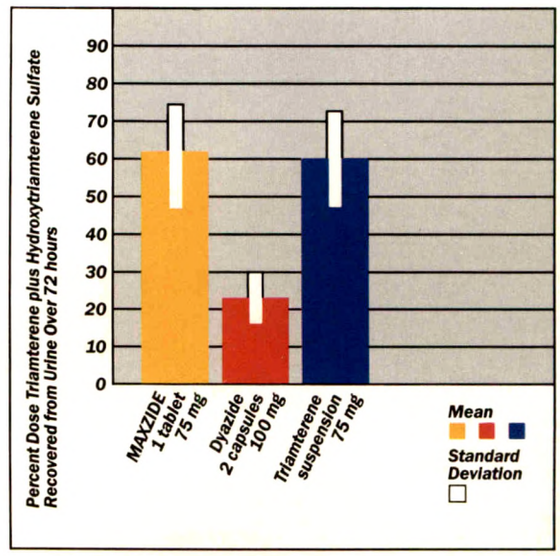
Percent dose of hydrochlorothiazide recovered from urine over 72 hours in subjects[a] given single oral doses



[a]Data from a study of 24 subjects.

[b]HydroDIURIL is the registered trademark of Merck & Co., Inc., for hydrochlorothiazide.

Percent dose of triamterene recovered from urine over 72 hours in subjects[a] given single oral doses



[a]Data from two studies of 24 subjects each.

NEW 1 tab q.d.

MAXZIDE™

Triamterene **75 mg**/Hydrochlorothiazide **50 mg**/Lederle

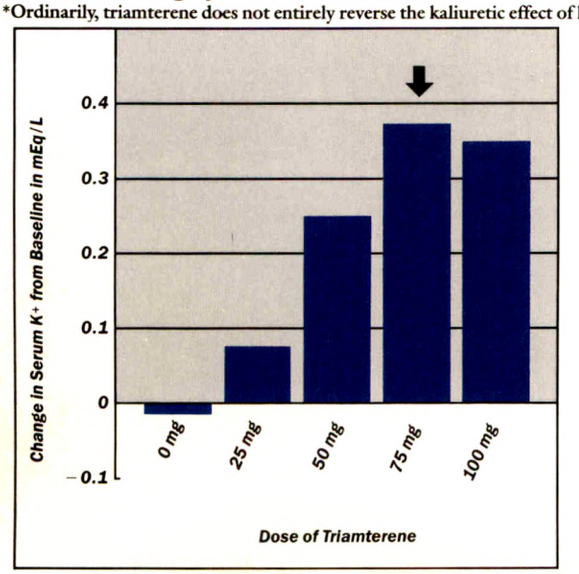
HYDROCHLOROTHIAZIDE EFFECTIVENESS WITH THE OPTIMAL DOSE OF TRIAMTERENE FOR POTASSIUM CONSERVATION

PROVEN FORMULATION MAXIMIZES POTASSIUM-SPARING EFFECT OF TRIAMTERENE

In a clinical dose-response evaluation, 75 mg triamterene daily most successfully corrected the hypokalemic effect of repeated daily doses of 50 mg hydrochlorothiazide.[3*]

Dose-response evaluation of triamterene's potassium-sparing activity in patients[a] rendered hypokalemic with long-term daily doses of 50 mg hydrochlorothiazide

*Ordinarily, triamterene does not entirely reverse the kaliuretic effect of hydrochlorothiazide.



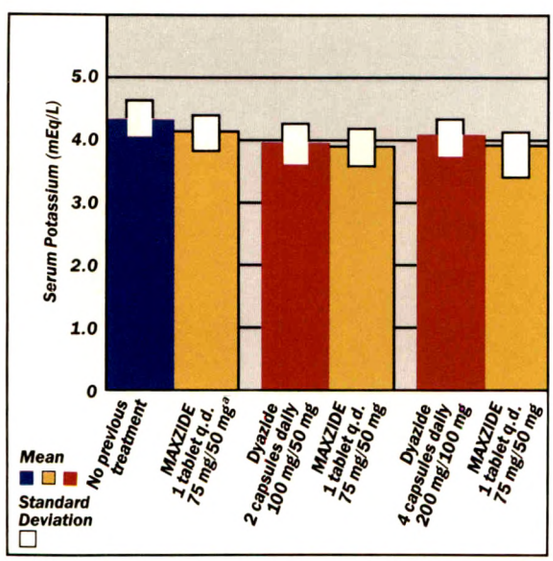
[a]Data from a study of 49 patients.

CLINICALLY SAFE AND WELL TOLERATED

MAXZIDE can be prescribed with confidence for patients transferred from Dyazide to provide the administered dose of hydrochlorothiazide while maintaining clinically acceptable serum potassium levels. Patients previously receiving no diuretic medication and patients previously taking up to four Dyazide capsules daily have been successfully treated with MAXZIDE q.d. with no compromise in clinical condition.[1†]

References: 1. Williams RL, Clark T, Blume CD: Clinical experience with a new combination formulation of triamterene and hydrochlorothiazide (Maxzide) in patients with mild to moderate hypertension. *Am J Med* 1984; 77(5A):62-66. 2. Blume CD, Williams RL, Upton RA, et al: Bioequivalency study of a new tablet formulation of triamterene and hydrochlorothiazide. *Am J Med* 1984; 77(5A):59-61. 3. Blume CD, Williams RL: A new antihypertensive agent: MAXZIDE. *Am J Med* 1984; 77(5A):52-58.

No clinically significant changes in serum potassium levels after 4 weeks of therapy with MAXZIDE one tablet q.d. in 138 patients previously untreated or transferred from Dyazide



[a]All dose ratios listed as triamterene in mg/hydrochlorothiazide in mg.

[†]Abnormal elevation of serum potassium levels (≥ 5.5 mEq/liter) can occur with all potassium-conserving diuretic combinations, including MAXZIDE. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), or in elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving MAXZIDE, when dosages are changed or with any illness that may influence renal function.

NEW *1 tab q.d.*

MAXZIDE™

Triamterene **75 mg**/Hydrochlorothiazide **50 mg**/Lederle

— FOR PATIENTS ON HYDROCHLOROTHIAZIDE WHO DEVELOP HYPOKALEMIA
— FOR NEWLY DIAGNOSED PATIENTS IN WHOM THE DEVELOPMENT OF HYPOKALEMIA CANNOT BE RISKED
— FOR PATIENTS TRANSFERRED FROM DYAZIDE

BRIEF SUMMARY

Please see package insert for full prescribing information.

INDICATIONS AND USAGE: *MAXZIDE is indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone. It is also indicated for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked (e.g., patients on digitalis preparations or with a history of cardiac arrhythmias, etc.).* ***This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.*** *MAXZIDE may be used alone or in combination with other antihypertensive drugs such as beta-blockers. Since MAXZIDE may enhance the actions of these drugs, dosage adjustments may be necessary. Usage in Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazards. Diuretics do not prevent development of toxemia in pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.*

CONTRAINDICATIONS: *Hyperkalemia: MAXZIDE should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq/liter). If hyperkalemia develops, this drug should be discontinued and a thiazide alone should be substituted. Concomitant use with other potassium conserving agents such as spironolactone, amiloride HCl or other formulations containing triamterene. Concomitant potassium supplementation in the form of medication, potassium-containing salt substitute or potassium-enriched diets should also not be used. Contraindicated in patients with anuria, acute and chronic renal insufficiency or significant renal impairment. Hypersensitivity to either component separately or other sulfonamide-derived drugs.*

WARNINGS: *Hyperkalemia.*

> *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium conserving agents including MAXZIDE. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), or elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving MAXZIDE, when dosages are changed, or with any illness that may influence renal function.*

If hyperkalemia is suspected, (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock) an electrocardiogram (ECG) should be obtained. Monitor serum potassium levels because mild hyperkalemia may not be associated with ECG changes. If hyperkalemia is present, MAXZIDE should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium level exceeds 6.5 mEq/liter, more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis. The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see CONTRAINDICATIONS). Patients with mild renal functional impairment should not receive this drug without frequent and continued monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide, the pharmacologically active metabolite of triamterene, and the sulfate ester of hydroxytriamterene have been shown to be reduced and the plasma levels increased following MAXZIDE administration to elderly patients and patients with impaired renal function. Hyperkalemia has been reported in diabetic patients with the use of potassium conserving agents even in the absence of apparent renal impairment. Avoid MAXZIDE in diabetic patients. If it is employed, serum electrolytes must be frequently monitored. Metabolic or Respiratory Acidosis: Potassium conserving therapy should also be avoided in severely ill patients in whom respiratory or metabolic acidosis may occur, since acidosis may be associated with rapid elevations in serum potassium levels. If MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg is employed, frequent evaluations of acid/base balance and serum electrolytes are necessary.

PRECAUTIONS: *Electrolyte Imbalance and BUN Increases: Patients receiving MAXZIDE should be carefully monitored for fluid or electrolyte imbalances, i.e., hyponatremia, hypochloremic alkalosis, hypokalemia and hypomagnesemia. Serum and urine electrolyte determinations should be frequently performed and are especially important when the patient is vomiting or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.*

Any chloride deficit during thiazide therapy is generally mild and usually does not require any specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypokalemia may develop with thiazide therapy, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids, ACTH, amphotericin B or after prolonged thiazide therapy. However, hypokalemia of this type is usually prevented by the triamterene component of MAXZIDE.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

MAXZIDE may produce an elevated blood urea nitrogen level (BUN), creatinine level or both. This is probably not the result of renal toxicity but is secondary to a reversible reduction of the glomerular filtration rate or a depletion of the intravascular fluid volume. Periodic BUN and creatinine determinations should be made especially in elderly patients, patients with suspected or confirmed hepatic disease or renal insufficiencies. If azotemia increases, MAXZIDE should be discontinued.

Hepatic Coma: MAXZIDE should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Renal Stones: Triamterene has been reported in renal stones in association with other calculus components. MAXZIDE should be used with caution in patients with histories of renal lithiasis. Folic Acid Deficiency: Triamterene is a weak folic acid antagonist and may contribute to the appearance of megaloblastosis in instances where folic acid stores are decreased. In such patients, periodic blood evaluations are recommended. Hyperuricemia: Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy. Metabolic and Endocrine Effects: The thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

Insulin requirements in diabetic patients may be increased, decreased or unchanged. Latent diabetes mellitus may become manifest during thiazide administration. Hypersensitivity: Sensitivity reactions to thiazides may occur in patients with or without a history of allergy or bronchial asthma.

Possible exacerbation or activation of systemic lupus erythematosus by thiazides has been reported. Drug Interactions: Thiazides may add to or potentiate the action of other antihypertensive drugs.

The thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown to increase responsiveness to tubocurarine.

Lithium, when given with diuretics, reduces renal clearance and increases the risk of lithium toxicity. Refer to the package insert on lithium before use of such concomitant therapy.

Acute renal failure has been reported in a few patients receiving indomethacin and other formulations containing triamterene and hydrochlorothiazide. Caution is therefore advised when administering nonsteroidal anti-inflammatory agents with MAXZIDE.

Drug/Laboratory Test Interactions: Triamterene and quinidine have similar fluorescence spectra; thus MAXZIDE may interfere with the measurement of quinidine.

Pregnancy: Category C: The safe use of MAXZIDE in pregnancy has not been established. Animal reproduction studies have not been conducted with MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg. It is also not known if MAXZIDE can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, pancreatitis, and possibly other adverse reactions which have occurred in the adult. MAXZIDE should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Thiazides appear in breast milk. If the use of MAXZIDE is deemed essential, the patient should stop nursing. Pediatric Use: The safety and effectiveness of MAXZIDE in children has not been established.

ADVERSE REACTIONS: *Side effects observed in association with the use of MAXZIDE include drowsiness and fatigue, insomnia, muscle cramps and weakness, headache, nausea, appetite disturbance, vomiting, diarrhea, constipation, dizziness, decreased sexual performance, shortness of breath and chest pain, dry mouth, depression and anxiety. These adverse reactions are common to other triamterene and hydrochlorothiazide containing products. Other adverse reactions include:*

Hydrochlorothiazide:

Gastrointestinal: anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. Central Nervous System: vertigo, paresthesias, xanthopsia. Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia, megaloblastosis. Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Hypersensitivity: anaphylaxis, purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis. Other: hyperglycemia, glycosuria, hyperuricemia, restlessness, transient blurred vision.

Triamterene:

Hypersensitivity: anaphylaxis, photosensitivity and rash. Other: Triamterene has been reported in renal stones in association with other calculus materials. Triamterene has been associated with blood dyscrasias. Whenever adverse reactions are moderate to severe, therapy should be reduced or withdrawn.

DOSAGE AND ADMINISTRATION: *The recommended dosage of MAXZIDE is one tablet daily with appropriate monitoring of serum potassium levels (see WARNINGS). Patients receiving 50 mg of hydrochlorothiazide who become hypokalemic may be transferred to MAXZIDE directly. In patients requiring 50 mg of hydrochlorothiazide in whom hypokalemia cannot be risked, therapy may be initiated with MAXZIDE. There is no clinical experience with doses exceeding one tablet daily.*

Clinical studies have shown that patients already taking less bioavailable formulations of triamterene and hydrochlorothiazide (totaling 50-100 mg of hydrochlorothiazide and 100-200 mg of triamterene) may be safely changed to one MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg tablet per day; these patients should be monitored clinically and with serum potassium after the transfer.

Lederle

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Wayne, New Jersey 07470

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Follow-Up After Coronary Arterial Reperfusion with Intravenous Streptokinase in Relation to Residual Myocardial Infarct Artery Narrowings

ROLF SCHRÖDER, MD, HANS VÖHRINGER, MD, THOMAS LINDERER, MD, GIANCARLO BIAMINO, MD, THOMAS BRÜGGEMANN, MSc, and ENZ-RÜDIGER V. LEITNER, MD

Short- and long-term changes in residual stenosis of the myocardial infarct-related coronary arteries in patients with successful reperfusion by intravenous streptokinase have not been determined until now. In 15 patients the residual diameter stenosis decreased significantly from 62 ± 9% after 24 hours to 55 ± 13% in the fourth week ($p < 0.005$). Quantitative angiographic analyses in 61 patients with patent infarct-related coronary arteries in the fourth week revealed a mean diameter stenosis of 61 ± 13%. The patients were followed up 34 ± 10 months. Sixteen had elective coronary artery bypass surgery or percutaneous transluminal coronary angioplasty (PTCA). Eighteen without coronary artery bypass surgery or PTCA had undergone repeat angiography after 26 ± 9 months. Twenty-five (41%) have had a residual diameter stenosis greater than 65% in the fourth week. A stenosis greater than 65% was found in: 4 of 5 patients with late reinfarction; 3 of 7 with 1-vessel coronary artery disease and persistent angina, compared with none of 11 with a stenosis less than 65%; 6 of 7, whose silent reocclusion had been found at long-term follow-up compared with 1 of 9 with a residual stenosis less than 65%. In 8 patients with persistent patency of the infarct artery, the stenosis had decreased significantly from 55 ± 6% to 36 ± 12% ($p < 0.005$). Correspondingly, there was a significant improvement in the infarct-related left ventricular wall motion disorders. These data indicate that in patients with less severe residual stenosis in the fourth week after successful intravenous streptokinase the long-term course is relatively uneventful, whereas reocclusion or reinfarction in the same myocardial territory is frequent in patients with a stenosis greater than 65%. PTCA may be advisable in these latter patients.

(Am J Cardiol 1985;55:313–317)

Anatomic studies have shown that a substantial percentage of lesions associated with vessel thrombosis in acute myocardial infarction are moderate in severity.[1,2] Successful thrombolysis can reestablish the coronary anatomy to its conditions before the acute thrombotic occlusion. On the basis of relatively limited information available, there are 2 conflicting attitudes about patients who have undergone successful thrombolytic reperfusion: (1) The affected coronary artery continues to pose the same hazard as before. Therefore, definite treatment requires additional mechanical therapy. (2) If sufficient anticoagulant therapy is given, patients are no different from others with myocardial infarction secondary to coronary artery disease (CAD).[3]

Short- and long-term changes in residual stenosis of the infarct-related coronary artery in patients with successful reperfusion by intravenous streptokinase (i.v. STK) have not been determined until now. In this study tentative answers are formulated on 4 questions: (1) What are the changes in the size of lesions that occur from 24 hours to the fourth week? (2) What is the clinical long-term course in relation to the residual diameter stenosis of the infarct-related coronary artery in the fourth week? (3) Can lesions that are liable to reocclude in the long-term course be identified? (4) To what extent are changes in the left ventricular wall motion disorders dependent from changes in size of coronary

From the Department of Cardiology and Pneumonology, Klinikum Steglitz, Free University Berlin, Berlin, Federal Republic of Germany. Manuscript received August 6, 1984; revised manuscript received October 15, 1984, accepted October 16, 1984.

Address for reprints: Professor Rolf Schröder, MD, Klinikum Steglitz, Freie Universität Berlin, Medizinische Klinik und Poliklinik, Hindenburgdamm 30, D 1000 Berlin 45, Federal Republic of Germany.

TABLE I Findings in the Fourth Week After Intravenous Streptokinase and Follow-Up Characteristics in 63 Patients with Patent Infarct-Related Coronary Arteries

	n	%
Angiography in the fourth week	75	
Successfully lysed	69	92
Reinfarction or reocclusion	6	8
Patent infarct artery	63	84
Follow-up 34 ± 10 mo	63	
Late cardiac death	6	10
Reinfarction	5	8
PTCA or CABG	16	25
Repeat angiography, no PTCA or CABG	19/44	43
Analyzable	18/44	41

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

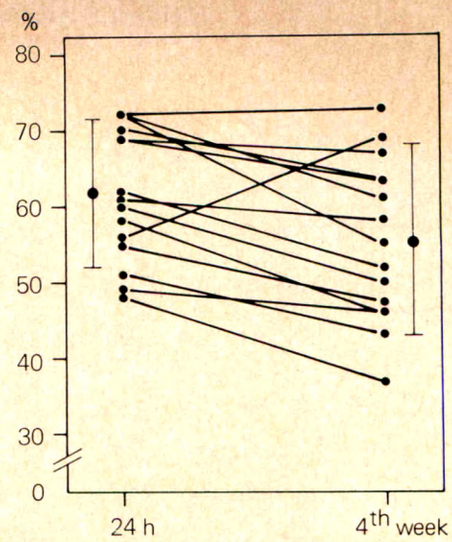

FIGURE 1. Changes in percent diameter stenosis from 24 hours after successful intravenous streptokinase to repeat angiography in the fourth week.

artery lesions occurring during the long-term follow-up?

Methods

Patients: From April 1980 to February 1982, 93 consecutive patients with symptoms and electrocardiographic findings typical of acute myocardial infarction were treated within 6 hours from the onset of chest pain. Forty-nine had a 30-minute i.v. infusion of 500,000 IU of STK and 44 received 1.5 million IU of STK infused within 60 minutes. In all patients 5,000 IU of heparin, 0.5 g of acetylsalicylic acid and 0.25 g of methylprednisolone were injected intravenously before STK. For the next 72 to 96 hours, heparin was infused at a dose sufficient to maintain a partial thromboplastin time at a 2 to 4 times control. Phenprocoumon treatment was initiated on the first or second day and continued for the next 3 weeks. After discharge from the hospital the patients were not treated routinely with anticoagulant therapy or antiplatelet drugs. Further details have been described elsewhere.[4]

In 15 patients with early restoration of coronary blood flow the area and luminal diameter of the most severe stenotic area of the infarct-related coronary artery was measured after 24 hours and in the fourth week. Because of the poor quality of some angiograms, quantitative analyses were not performed immediately after successful lysis. Seventy-five patients underwent angiography during the fourth week after acute myocardial infarction (Table I). Sixty-three patients who revealed a patent infarct-related coronary artery were followed up for a mean of 34 ± 10 months (range 3 to 49). Six patients were followed up until they died.

Nineteen patients who did not undergo coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) underwent repeat angiography during follow-up. In 18 patients the quality of the angiograms was sufficient for quantitative analysis. There was no patient selection because all patients had been asked to undergo repeat angiography. There was no difference between those who agreed to a repeat study and those who did not with respect to 2- or 3-vessel CAD, impairment of left ventricular function in the fourth week, clinical signs of cardiac failure or angina pectoris.

Quantitative angiographic analysis: The technique of analysis has been described previously.[4,5] Briefly, the most severe stenotic area of the infarct-related coronary artery was analyzed from 2 to 5 cineprojections at end-diastole. Each of these views was projected on a large screen and was carefully traced on a digitizer tablet with as much of the adjacent vessel as could be seen in either view. The mean values of the area and the diameter stenosis were digitally computed for all measurements.

The left ventricular wall motion disorders were calculated from a left ventricular angiogram in a 30° right anterior oblique projection by a computer-constructed polar coordinate system. Excluding the aortic valve plane, the computer divided the silhouettes into 48 segmental radii with equal angles. The end-diastolic and end-systolic contours were superimposed using a fixed reference system. The results were printed out as numerical data and a histogram of percent shortening of the systolic segmental radii. Segmental radii shortening less than one-third of the normal range of systolic shortening in healthy subjects was considered an akinetic segment.

In 2 patients, stenoses could not be measured quantitatively; 1 of them subsequently died, and the other had an uncomplicated course. In the latter patient, the angiogram at repeat study could not be analyzed.

Statistical analysis: Data are expressed as mean ± standard deviation. Paired or unpaired Student *t* tests were applied to the coronary artery lesions and wall motion abnormalities whenever appropriate.

Results

Patency of the infarct-related artery, 24 hours to 4 weeks: Figure 1 shows the changes in the diameter stenosis from 24 hours after successful i.v. lysis to the fourth week. There was a significant decrease, from 62 ± 9% to 55 ± 13% ($p < 0.005$). The corresponding area stenosis decreased from a mean value of 84 ± 8% to 79 ± 13% ($p < 0.01$). None of the 15 patients had reocclusion, but in 1 the diameter stenosis increased to greater than 65% in the fourth week and in 2 it remained above 65%. In 1 of these 3 patients subsequent successful PTCA has been performed. In the other 2, the infarct-related artery was found occluded at repeat angiography several months later.

Clinical long-term course in relation to residual infarct artery lesions: The clinical outcome of the 75 patients with angiography in the fourth week are listed

TABLE II One-Vessel or Multivessel Coronary Artery Disease and Persistent Angina Pectoris in Patients with Uncomplicated Long-Term Course

	1-Vessel CAD	Multivessel CAD
Pt No.	18	18
Stenosis >65%	7	4
Angina	3	5
Angina, stenosis >65%	3 (70, 72, 74%)	1 (71%)

CAD = coronary artery disease.

in Table I. According to angiographic observation during the acute phase (16 patients) or early elevation of serum CK-MB and a significantly earlier peak in the serial serum CK-MB activity curve (53 patients), successful restoration of coronary blood flow was achieved in 69 patients (92%). One patient had a reocclusion after 24 hours, and 5 without angiography in the acute phase had early reinfarction. In these 6 patients the infarct-related coronary artery was occluded in the fourth week.

Of the 63 patients with patent infarct-related arteries in the fourth week, 21 had 1-vessel, 25 had 2-vessel and 17 had 3-vessel CAD. Thirteen patients underwent elective CABG 1.8 ± 1.3 months after the acute infarction; 1 to 5 grafts (mean 3 ± 1) were placed. Two patients had early elective PTCA. One patient underwent late PTCA 38 months after his infarct. Fourteen of these 16 patients had multivessel CAD; all had angina despite intensive medical therapy.

During long-term follow-up 6 patients died from cardiac causes, 4, 5, 10, 15, 16 and 28 months after myocardial infarction, the last 26 months after CABG. Five patients died suddenly and 1 patient died from cardiogenic shock after reinfarction. Five reinfarctions occurred at the site of the previous infarct, 5 and 6 weeks as well as 6, 26 and 38 months after the first infarction.

Thirty-seven patients had a clinically uncomplicated long-term course. When present, angina was sufficiently controlled by medical therapy. However, during exercise electrocardiography 27 ± 7 months after infarction and interrupted medical therapy, 8 patients experienced angina at a mean workload of 1.2 ± 0.3 (0.75 to 1.7) w/kg body weight (Table II).

Figure 2 lists the individual data, mean and standard deviations of the diameter stenosis of the infarct-related artery measured in the fourth week after successful i.v. STK. For 1 patient who subsequently died and 1 with an uncomplicated course, quantitative analysis could not be performed. The average residual diameter stenosis in 61 patients was 61 ± 13%.

In the 16 patients who underwent CABG or PTCA, the mean diameter stenosis was 67 ± 9%. Eight of these 16 patients had a stenosis greater than 65%. In patients who had a reinfarction during follow-up, the diameter stenosis in 4 of 5 was greater than 65%.

Thirty-six patients with clinically uncomplicated long-term follow-up had a residual diameter stenosis of 58 ± 13%. Eighteen patients had 1-vessel CAD, 7 of whom had a residual diameter stenosis greater than 65%

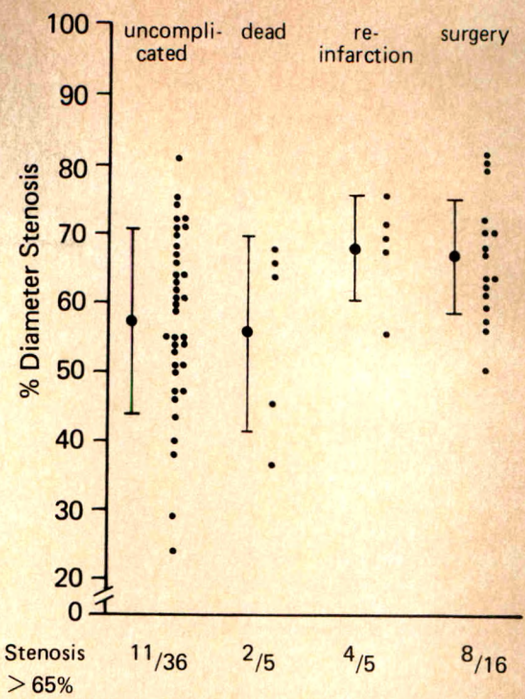

FIGURE 2. Individual data and mean ± standard deviation of diameter stenosis of the infarct artery in the fourth week in relation to the long-term course.

of the infarct-related coronary artery. After discontinuation of medical treatment, 3 of these 7 patients had angina on exertion, whereas none of 11 with a residual diameter stenosis less than 65% had angina (Table II).

In 5 patients with late cardiac death, the diameter stenosis in the fourth week did not differ from that in patients with an uncomplicated course. However, all patients who subsequently died had multivessel CAD and severe left ventricular impairment. The ejection fraction was 39 ± 16%, compared with 60 ± 12% in patients who survived.

Patency of the infarct-related vessel, chronic stage, fourth week to follow-up: Figure 3 shows the changes in diameter stenosis from the fourth week to repeat study 26 ± 9 months later in 18 patients who had no CABG or PTCA. In 2 patients with longer, extended and subtotal occlusion and opacification of the peripheral parts of the vessel mostly through collateral vessels (i.e., functional occlusion), the arteries were considered occluded.

Eight patients had a diameter stenosis greater than 65% in the fourth week. In 6 patients, the infarct artery was occluded, although there had been no clinical signs of reinfarction. Two patients have had reinfarctions. One patient with a high-grade stenosis of a diagonal branch underwent repeat study after an uneventful course of 27 months, and the coronary artery lesion was almost the same. The patient was free of symptoms and had a negative exercise electrocardiogram up to 200 W. Ten months later he had a reinfarction, which was successfully treated with i.v. STK. Angiography the next day showed that the infarct artery was patent, but the size of the residual diameter stenosis was 72%,

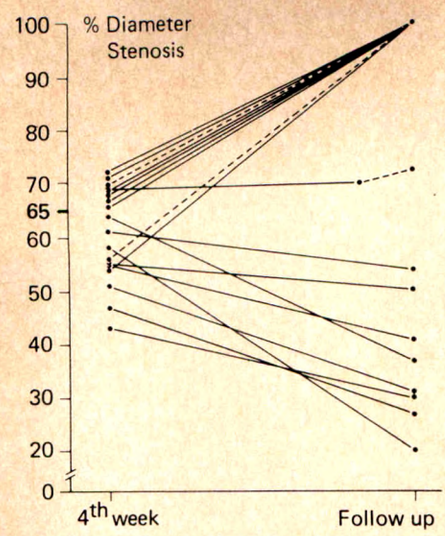

FIGURE 3. Changes in diameter stenosis from the fourth week to repeat study 26 ± 9 months later in patients without coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. **Broken lines** represent patients who had a reinfarction in the interval.

compared with 69% 10 months before. Successful PTCA was performed in the same setting.

Ten patients had a residual diameter stenosis of less than 65% in the fourth week after the acute event. In 8, during follow-up, the stenosis decreased significantly from a mean value of 55 ± 6% to 36 ± 12% ($p < 0.005$). In 2 patients the infarct-related coronary artery was occluded; of these patients 1 had had a reinfarction. Both patients had multivessel CAD and more than 1 stenosis of the infarct-related coronary artery. CABG had been recommended to both patients, but both had refused.

Changes in left ventricular wall motion disorders, chronic stage, fourth week to follow-up: Figure 4 shows the changes in the left ventricular function during follow-up in patients with a diameter stenosis less than 65% in the fourth week. One patient with 3-vessel CAD and a second infarction different from the localization of the previous infarct is excluded. There was a decrease in the infarct-related number of akinetic segments from 7.2 ± 5 to 4.2 ± 7 ($p < 0.05$). In the 7 patients with patent infarct-related coronary arteries, the number of akinetic segments decreased from 5.9 ± 3 to 0.7 ± 1 ($p < 0.005$). In these 7 patients the ejection fraction increased from 56 ± 7 to 63 ± 9% ($p < 0.05$).

Figure 5 shows the changes in the number of akinetic segments in the 8 patients with a diameter stenosis greater than 65% in the fourth week. On the average, there was no change in the number of akinetic segments (4.3 ± 6 to 3.8 ± 4). Although their infarct-related coronary arteries were found occluded during follow-up, 3 showed considerable improvement, probably because sufficient collateral flow had developed.

Discussion

The appearance of a lesion immediately after reperfusion with intracoronary (i.c.) STK does not reflect the eventual size of the underlying fixed lesion. Further increase in the luminal diameter after 1 or more weeks compared with immediate post-i.c. STK has been shown.[6–9] Our findings in 15 patients with successful i.v. STK indicate that the extent of residual stenosis may substantially decrease even after 24 hours. In only 3 of 15 patients was there no decrease or increase in the remaining stenosis of the infarct-related coronary artery in the fourth week compared with that 24 hours after the acute event. Possible reasons for late changes in the size of stenosis after reperfusion with STK were thoroughly discussed by Harrison et al.[9]

In the fourth week after successful i.v. STK, quantitative analysis of the infarct-related coronary artery revealed a residual diameter stenosis of 61 ± 13%. This finding is in keeping with the results obtained by quantitative angiographic analysis 2 weeks after successful i.c. STK.[8,9] However, more severe residual stenosis of the recanalized coronary artery by i.c. STK have

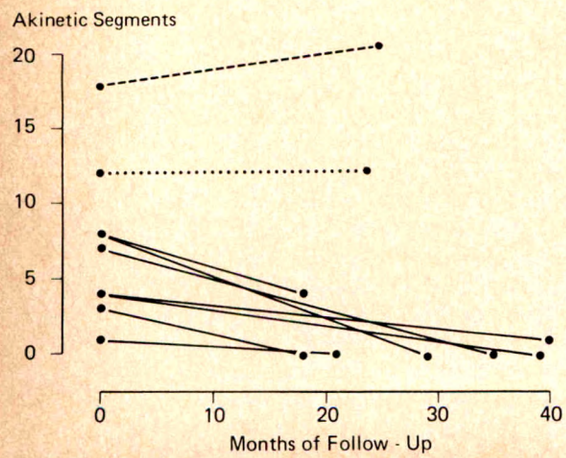

FIGURE 4. Changes in number of akinetic segments during follow-up in patients with a diameter stenosis less than 65% in the fourth week. **Broken line** indicates patient who had reinfarction in the interval. **Dotted line** indicates patient whose infarct-related artery was found to be occluded ("silent occlusion").

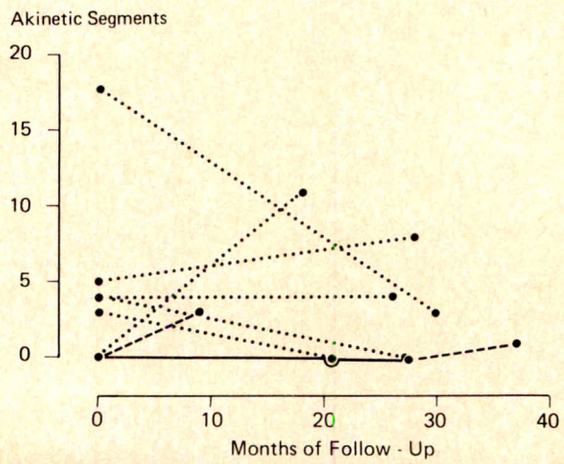

FIGURE 5. Changes in the number of akinetic segments during follow-up in patients with a diameter stenosis greater than 65% in the fourth week. **Broken line** indicates patient who had reinfarction in the interval. **Dotted line** indicates patients whose infarct-related artery was occluded ("silent occlusion").

been reported.[10,11] These reports are based on subjective interpretation of the stenotic lesions. Overestimation and excessive variations by intra- or interobserver error have been reported. Some reports suggest that the traditional analysis of coronary angiograms is inadequate for determining significance of coronary stenosis.[8,9] When histologic sections of patients with transmural acute myocardial infarction and coronary artery thrombi[12] are compared with cross-sectional areas derived from diameter measurements after lysis, the quantitative angiographic results from Serruys et al,[8] Harrison et al,[9] and ours in vivo are consistent with the histologic findings.

The optimal management course after successful thrombolytic therapy has not been defined. An incidence of more than 20% of reinfarctions and late reocclusions after successful i.c. STK treatment has been reported.[8,13–15] Therefore, additional PTCA immediately after i.c. STK[8,15,16] or CABG[17,18] has been advocated. However, the observation that the extent of residual stenosis may decrease spontaneously and that the early reocclusion rate after PTCA may be as high as 20%[19] emphasizes that the true value of additional PTCA remains to be assessed.

In patients with high-dose i.v. STK of brief duration, early reinfarction rates tended to be lower.[4,20–22] The early reocclusion and reinfarction rates may be in the same order as in patients with i.c. STK and additional PTCA.[8,9,19,23,24] However, the long-term course tended to be more complicated in patients with a more severe residual stenosis. Four of 5 patients who sustained a late reinfarction had a residual diameter stenosis greater than 65% in the fourth week. Three of 7 patients with 1-vessel CAD and a stenosis greater than 65% had persistent angina pectoris on exertion; none of 11 had less severe stenosis.

Although our results are limited by the small number of patients studied, it appears that vessels with a residual diameter stenosis greater than 65% in the fourth week frequently reocclude during long-term follow-up. Late reocclusion may not imply reinfarction or worsening of the left ventricular function. On the contrary, there may be considerable improvement. However, even retrospectively we were unable to predict the particular patient's risk.

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Value of Radionuclide Angiography for Predicting Specific Cardiac Events After Acute Myocardial Infarction

KENNETH G. MORRIS, MD, SEBASTIAN T. PALMERI, MD, ROBERT M. CALIFF, MD, RAY A. McKINNIS, PhD, MICHAEL B. HIGGINBOTHAM, MB, R. EDWARD COLEMAN, MD, and FREDERICK R. COBB, MD

The value of rest and exercise radionuclide angiography (RNA) for predicting specific events including death, recurrent acute myocardial infarction (AMI), coronary care unit readmission for unstable chest pain, and medically refractory angina after AMI was studied in 106 consecutive survivors of AMI. Analysis of the RNA variables using the Cox proportional hazards regression model yielded significant associations of the time to death with ejection fraction at rest and during exercise (χ^2 = 11.1 and 14.0, respectively). Both variables added significant prognostic information to the clinical assessment (χ^2 = 4.3 and 5.7, respectively). The change in ejection fraction from rest to exercise predicted the time to coronary artery bypass grafting for medically refractory angina before (χ^2 = 21.0) and after (χ^2 = 13.2) adjustment for the clinical descriptors, but did not predict death or other nonfatal events. Significant correlations were found between RNA variables and a variety of clinical descriptors previously reported to have prognostic significance. Clinical and RNA variables that are measures of left ventricular function were predictive of subsequent mortality, whereas those that reflect residual potentially ischemic myocardium were predictive of subsequent nonfatal ischemic events. Rest and exercise RNA after AMI provides significant prognostic information regarding specific events during follow-up independent of that provided by clinical assessment.

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A variety of clinical and laboratory variables have prognostic significance in survivors of acute myocardial infarction (AMI). The underlying pathophysiology reflected by these variables appears to be predominantly the severity of left ventricular (LV) dysfunction produced by AMI or the presence of potentially ischemic myocardium. Variables such as Killip class, cardiomegaly, infarct location and exercise time that correlate with the severity of LV dysfunction after AMI have been reported to have prognostic significance.[1–8] Studies have shown that among clinical and contrast angiographic variables, ejection fraction (EF) at rest, a direct measure of LV function, is the most important predictor of mortality after AMI.[9,10] Other prognostic variables such as recurrent angina pectoris, exercise stress testing variables,[11–13] and the angiographic severity of coronary artery disease (CAD)[10] are indicators of myocardium that may become ischemic. Radionuclide angiography is a noninvasive method of evaluating LV function at rest and exercise,[14] and is more sensitive than ST-segment changes for detecting significant CAD.[15] Thus, rest and exercise RNA is an attractive procedure for risk assessment after AMI because it provides noninvasive measurements of both the severity of LV dysfunction and the presence of potentially ischemic myocardium.

The purpose of the present study was to ascertain the relation of specific rest and exercise RNA measurements with specific follow-up events and to determine their value added to other clinical variables for predicting mortality, recurrent AMI, and unstable or medically refractory angina in follow-up in a prospective study of survivors of AMI.

From the Department of Medicine, Division of Cardiology and the Department of Radiology, Duke University Medical Center and the Durham Veterans Administration Medical Center, Durham, North Carolina. This study was supported in part by Research Grant HL 17670 from the National Heart, Lung and Blood Institute, Bethesda, Maryland; HS03834 from the National Center for Health Services Research–OASH, Hyattsville, Maryland; the Henry J. Kaiser Family Foundation, Menlo Park, California; The Andrew W. Mellon Foundation, New York, New York; and by the Research Service of the Durham Veterans Administration Medical Center, Durham, North Carolina. Manuscript received September 14, 1984; revised manuscript received October 24, 1984, accepted October 25, 1984.

Address for reprints: Frederick R. Cobb, MD, Division of Cardiology (111A), Durham Veterans Administration Medical Center, 508 Fulton Street, Durham, North Carolina 27705.

TABLE I Baseline Characteristics (Clinical Class)

		I	II	III	IV
Worst Killip class	3 wks post-MI	64	32	8	2
NYHA class angina	3 wks post-MI	49	22	17	18
NYHA class CHF	3 wks post-MI	72	22	10	2

CHF = congestive heart failure; MI = myocardial infarction; NYHA = New York Heart Association.

Methods

Patients: A prospective consecutive series of 165 patients admitted to the coronary care unit of the Durham Veterans Administration Medical Center with documented myocardial infarction manifest by chest pain and positive myocardial creatine kinase isoenzymes was evaluated for this study. Seventeen patients died within 21 days of AMI and were excluded from the study group. Eighteen patients were excluded from the study because of valvular heart disease, chronic renal insufficiency, metastatic malignancy or other serious comorbid disease. Fifteen patients refused participation in the study. Nine patients could not exercise because of severe congestive heart failure, lower extremity amputation or unstable pain. One hundred six patients constituted the study group.

Study protocol: The study protocol consisted of RNA at rest and during upright bicycle exercise 3 weeks after AMI. Exercise was performed on a bicycle ergometer in the postabsorptive state. Beta-adrenergic blocking drugs were tapered and discontinued 48 hours before study. Nitrates were withheld 6 hours before study. Exercise was initiated at 100 or 200 kpm and increased by 100 kpm each minute. Heart rhythm was monitored continuously and standard limb leads and V_5 and V_6 electrocardiograms were recorded at rest and at each minute of exercise. Exercise endpoints were a maximal heart rate of 120 beats/min, chest pain, significant ST depression or severe fatigue. RNA was performed in the sitting position before exercise and at peak exercise. Clinical assessment included New York Heart Association (NYHA) functional class for angina and congestive heart failure and ST-segment changes and chest pain during exercise.

Radionuclide angiography: Gated equilibrium RNAs were acquired over $1\frac{1}{2}$ to 2 minutes after in vivo red cell labeling with technetium-99m using a Siemens L.E.M. gamma camera and an r-wave-triggered gate interfaced to an MDS modumed or A^2 computer system. Data were analyzed in a 64 × 64 matrix as twenty-eight 100,000 count frames. A semiautomated edge detection algorithm (A2MUGE, MDS) was used to outline the LV region of interest for each frame. A varying region-of-interest technique was then used for construction of a volume curve after background correction for calculation of the EF. Wall motion abnormalities were evaluated qualitatively by consensus from an endless loop display. Each RNA was divided into septal, inferoapical and posterolateral segments and each was scored as 0 (normal), 1 (mild hypokinesia), 2 (severe hypokinesia), 3 (akinesia) and 4 (dyskinesia). Patients with higher scores at exercise than at rest in any region were considered to have exercise-induced abnormalities.

Therapy and follow-up: The results of RNA testing were not reported to the physicians treating the patients or used for therapeutic decision-making. Beta-adrenergic blocking agents were not used prophylactically, but were given for significant angina. Patients with refractory angina or positive treadmill stress tests at low workloads (stage I or II, Bruce protocol) underwent coronary angiography. Only patients with refractory NYHA class III or IV angina or left main coronary stenosis greater than 50% underwent bypass grafting.

TABLE II Baseline Characteristics (Complications of Infarction)

Infarct extension	7
Radiographic cardiomegaly	30
Mobitz II 2° AVB	1
Complete heart block	0
Atrial tachyarrhythmias	
Persistent sinus tachycardia	17
Paroxysmal atrial tachycardia	3
Atrial flutter	5
Atrial fibrillation	6
Ventricular arrhythmias	
6 PVCs/min (1st 48 hours)	15
6 PVCs/min (>48 hrs)	8
Ventricular tachycardia	14
Ventricular fibrillation	5

2° AVB = second-degree atrioventricular block; PVCs = premature ventricular complexes.

Two patients had significant left main CAD but also had class IV angina.

Patients were followed either by clinic appointment or by telephone with regard to mortality, functional class for angina pectoris, hospitalization for myocardial infarction or unstable angina, and coronary artery bypass grafting (CABG) for disabling angina refractory to medical therapy. The minimal duration of follow-up was 24 months. All recurrent infarcts were documented by new electrocardiographic Q waves or enzyme measurements. Patients were readmitted to the coronary care unit for unstable angina, defined as recurrent episodes of prolonged chest pain or a marked progression in the frequency and severity of their chest pain syndrome.

Data analysis: The strengths of associations between RNA measurements and individual clinical variables were determined using the Spearman rank correlation coefficient.

The value of rest EF, exercise EF, the change in EF from rest to exercise, and exercise-induced wall motion changes was analyzed for predicting 4 specific events in follow-up. These included death, recurrent nonfatal infarction, CABG for medically refractory disabling angina pectoris, and admission to the coronary care unit for unstable angina. Because the pathophysiology of the various events may be different, each event was analyzed separately and no events were combined for analysis. When nonfatal events were analyzed the follow-up of patients who died was censored at the time of death.

For all prognostic analyses, associations between each RNA variable and the time to an event were determined using Breslow's formulation of the Cox proportional hazards regression model.[16,17] The log likelihood ratio chi-square statistic of the univariable model was first used to assess the significance of the relation between each RNA variable and the time to each event. This analysis was then extended to determine whether RNA measurements contributed information beyond that available using clinical parameters. For this analysis, a 2-step model was used in which the combined significance of the clinical variables was considered first in the proportional hazards regression model; the added value of the

TABLE III Correlation Between Radionuclide Angiographic and Clinical Prognostic Variables

	Rest EF	Exercise EF	ΔEF	Wall Motion Δ
Age	0.00	−0.15	−0.26†	0.12
Anterior MI	−0.46‡	−0.42‡	0.00	0.03
Inferior MI	0.23*	0.31‡	0.21*	−0.09
Killip class	−0.33‡	−0.38‡	−0.14	−0.12
MI extension	−0.03	−0.08	−0.11	0.07
Previous MI	−0.18	−0.26†	−0.14	0.04
Cardiomegaly	−0.25†	−0.24*	0.02	−0.01
Functional class angina	0.11	0.01	−0.09	0.14
Functional class CHF	−0.28†	−0.26†	−0.02	−0.05
Atrial tachyarrhythmia	−0.17	−0.15	0.04	−0.18
Ventricular arrhythmia	−0.16	−0.15	−0.04	−0.14
Exercise ST depression	0.09	−0.07	−0.29†	0.16

Spearman correlation coefficients: * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.
CHF = congestive heart failure; EF = ejection fraction; ΔEF = changes in EF from rest to exercise; MI = myocardial infarction; Wall Motion Δ = exercise-induced wall motion abnormalities.

RNA variable of interest was then examined. To determine the statistical significance of the added contribution of each RNA variable, the difference in model log likelihood ratio chi-square using the clinical variables alone was compared with the chi-square value using both the clinical variables and the RNA variables. The clinical variables that were used included age, previous infarction, infarct location, worst Killip class, infarct extension, cardiomegaly, ventricular arrhythmias and atrial tachyarrhythmias during the acute infarct period, NYHA functional class for angina and congestive heart failure, and the occurrence of ST depression (at least 0.1 mV) with exercise. Atrial tachyarrhythmias were analyzed together as a single dichotomous variable. Ventricular arrhythmias were graded as an index with the following weight: 2 points for ventricular fibrillation, 1 point for ventricular tachycardia, ½ point for at least 6 premature ventricular contractions per minute after the first 48 hours and ¼ point for at least 6 premature ventricular contractions per minute in the first 48 hours. Because of the small number of coronary artery bypass procedures during the follow-up period, only the most significant clinical variables, i.e., worst Killip class, infarct location, functional class for angina, and ST depression with exercise, were included in the adjusted models for medically refractory angina.

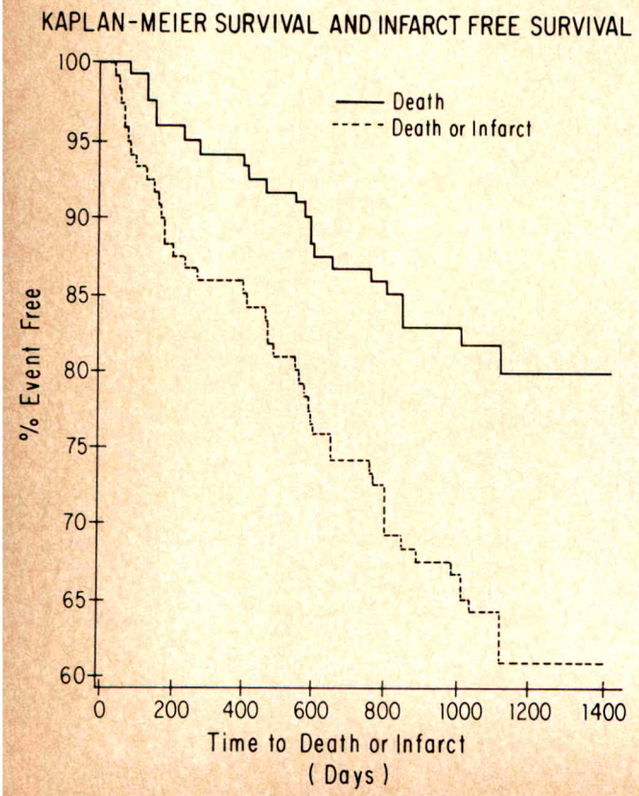

FIGURE 1. Life-table survival and infarct-free survival of the patient population.

Results

Baseline characteristics: The 106 patients (105 men, 1 woman) studied were 31 to 84 years old (mean 56). The electrocardiographic location of AMI was anterior in 31, inferior in 40, inferior and anterior in 2, undetermined in 1 (with left bundle branch block), and "subendocardial," i.e., not accompanied by new Q waves, in 32; 37 had a history of AMI. The frequency of other selected baseline characteristics of the population is summarized in Tables I and II.

Clinical outcomes: Figure 1 shows the rate of cardiac deaths and recurrent AMI. By 1 year of follow-up, 15% of patients had either died or sustained a recurrent AMI and by 2 years of follow-up 27% had 1 of these major cardiac events. During the follow-up period, 24 patients died. Fifteen deaths were sudden, 2 deaths were associated with progressive congestive heart failure, 4 occurred within a few days of a documented recurrent AMI, 2 occurred in hospital with heart failure or ventricular fibrillation shortly after a prolonged episode of chest pain and 1 patient had a fatal cerebrovascular accident. During the same period of follow-up 20 patients had recurrent nonfatal AMI, 21 were readmitted to the coronary care unit with unstable chest pain and 10 underwent CABG for disabling medically refractory angina pectoris. Thirty-eight patients had 1 or more of these nonfatal events.

Relation of radionuclide angiographic variables to clinical descriptors: Table III is a summary of correlations between the RNA variables and selected clinical variables that have been reported to be of prognostic significance. In general, rest and exercise EF correlated inversely with variables that reflect diminished LV function, such as history of infarction, anterior infarction, Killip class, cardiomegaly and the functional

class for congestive heart failure. The change in EF from rest to exercise correlated inversely with the occurrence of exercise-induced ST-segment depression. Exercise-induced wall motion abnormalities did not correlate with any clinical variable.

Predictors of mortality: Table IV is a summary of the results of Cox model analysis of the relation among the RNA and clinical variables and the time to each event. Both rest and exercise EF were correlated inversely with subsequent mortality; exercise EF had a higher chi-square value (14.0, $p < 0.001$) than the rest value ($\chi^2 = 11.1$, $p < 0.001$). When the aggregate significance of only the clinical variables was considered in a multivariable model, a chi-square value of 24.9 was obtained. However, the 12 degrees of freedom (d.f.) necessary in this multivariable model reduced the level of significance ($p = 0.02$). Thus, both RNA EF measurements achieved a higher level of significance than the combination of clinical variables. Worst Killip class and history of infarction were the most significant clinical variables; chi-square values were 5.23 and 3.83 (1 d.f.), respectively, after adjustment for the other clinical descriptors. When the RNA variables were examined to determine the amount of prognostic information, they provided beyond that contained in the clinical data, both exercise and rest EF yielded significant independent prognostic information ($\chi^2 = 5.7$ and 4.3, respectively). When both rest and exercise EF were included in a bivariable model, only the exercise value remained significant.

To further illustrate the added value of the RNA over the clinical variables, the patients were separated into high- and low-risk groups on the basis of clinical characteristics. Patients with ventricular fibrillation or tachycardia, Killip class III or IV, supraventricular tachyarrhythmia or infarct extension were classified as high risk. Among the 80 patients with at least 1 of these high risk indicators, mortality was 48% (14 of 29) in patients with exercise EF of 40% or less, compared with 10% (5 of 51) with exercise EF of more than 40%. Of the 26 patients considered to be at low risk by the absence of any of these clinical criteria, 5 had an exercise EF of 40% or less and 2 of these patients (40%) died during follow-up, compared to only 14% (3 of 21) with exercise EF more than 40%.

The change in EF from rest to exercise was not significantly associated with the time to death. Since previous studies have demonstrated an inverse relation between rest EF and the change in EF with exercise,[18,19] patients with EF less than 30% were excluded from a second analysis in an attempt to improve the predictive value of the change in EF with exercise. Among the 86 patients with a rest EF of more than 30%, 14 died during the follow-up period; however, the change in EF from rest to exercise was not associated with the time to death, even in this subgroup of patients. The occurrence of exercise-induced wall motion abnormalities, another variable related to myocardial ischemia, also was not significantly associated with the time to death.

The 2-year mortality predicted by the Cox regression model from exercise EF alone is shown in Figure 2. As EF fell below 45%, mortality increased dramatically. Thus, the expected mortality at 2 years was 11% with

TABLE IV Prognostic Significance of Radionuclide Angiographic Variables for Subsequent Events

	Death (n = 24)				Nonfatal MI (n = 20)				Unstable Angina (n = 21)				Refractory Angina (n = 10)			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p
Rest EF	11.1	0.001*	4.3	0.04*	0.0	0.84	0.0	1.00	0.4	0.53	1.7	0.19	0.4	0.55	0.1	0.82
Exercise EF	14.0	0.001*	5.7	0.02*	0.1	0.76	0.1	0.76	1.5	0.22	0.9	0.35	2.1	0.15	3.8	0.05*
ΔEF	1.1	0.29	0.3	0.60	1.6	0.21	0.5	0.49	2.2	0.13	0.1	0.82	21.1	0.001*	13.2	0.001*
Exercise wall motion Δ	0.2	0.64	0.1	0.76	4.1	0.04*	3.3	0.07	2.2	0.14	0.1	0.79	4.2	0.04*	2.0	0.15
Clinical variables			24.9 (12 d.f.)	0.02*			9.2 (12 d.f.)	0.68			24.5 (12 d.f.)	.02*			8.3 (4 d.f.)	0.08

n = number of events; χ^2 = likelihood ratio chi-square with 1 degree of freedom except where indicated. (The multivariable χ^2 for each parameter is an assessment of prognostic significance, adjusted for clinical variables.); other abbreviations as in Table III.

* $p \leq 0.05$.

an exercise EF of 50%, 29% with an exercise EF of 30% and 56% with an exercise EF of 15%. Figure 3 shows the same relation in a different fashion, by comparing the Kaplan-Meier survival curve of patients with an exercise EF less than 40% to the survival curve of patients with an exercise EF of at least 40%.

Nonfatal infarction: The time to nonfatal AMI was associated only with the development of exercise-induced wall motion abnormalities ($\chi^2 = 4.1$). After adjustment for the 12 clinical descriptors, this relation was not statistically significant. The time to nonfatal AMI was not significantly associated with the clinical variables.

Unstable angina: The time to coronary care unit admission for unstable chest pain was not associated with any of the RNA variables. The clinical variables were significantly associated with subsequent readmission of the coronary care unit for unstable angina ($\chi^2 = 24.5$, 12 d.f., $p = 0.02$). NYHA classes for angina and congestive heart failure 3 weeks after infarction were the most significant variables (adjusted χ^2 [1 d.f.] = 5.22 [$p = 0.02$] and 8.51 [$p = 0.004$], respectively).

Disabling refractory angina: The time to CABG for disabling refractory angina was highly associated with the change in EF from rest to exercise before and after adjustment for clinical descriptors; the chi-square values (1 d.f.) were 21.08 and 13.19, respectively. The time to CABG for medically refractory angina was significantly associated with exercise-induced wall motion abnormalities, but the relation was not significant after adjustment for the clinical variables. The 4 clinical variables also were not significantly associated with this endpoint.

Discussion

In this study, rest and exercise EF were the most important predictors of subsequent mortality among the variables studied. EF during exercise was the most potent predictor of mortality. Exercise EF is the sum of the rest EF and the change in EF during exercise and thus reflects the amount of infarcted myocardium as well as the myocardium at risk for further ischemia or AMI. Exercise EF contained all of the prognostic information present in the rest value. The rigorous statistical analysis shows that both variables provided prognostic information beyond that available from clinical assessment. Furthermore, several clinical variables that have been associated with increased mortality in previous studies also correlated with a reduced EF. These included variables such as worst Killip class, NYHA functional class for congestive heart failure, cardiomegaly, and infarct location, which might be anticipated to relate to the severity of LV dysfunction. The prognostic value of certain clinical variables thus appears to result from their relation to the severity of LV dysfunction.

The 2 RNA variables most specifically related to exercise-induced ischemia, the change in EF from rest to exercise and exercise-induced wall motion abnormalities, were not significant univariate predictors of subsequent mortality. Several points should be considered in interpreting the lack of a relation in this study between the change in EF with exercise and subsequent mortality. We observed that in a population of patients with CAD the change in EF with exercise is inversely related to the rest EF.[18,19] Consequently, subjects with normal rest function have the highest likelihood of

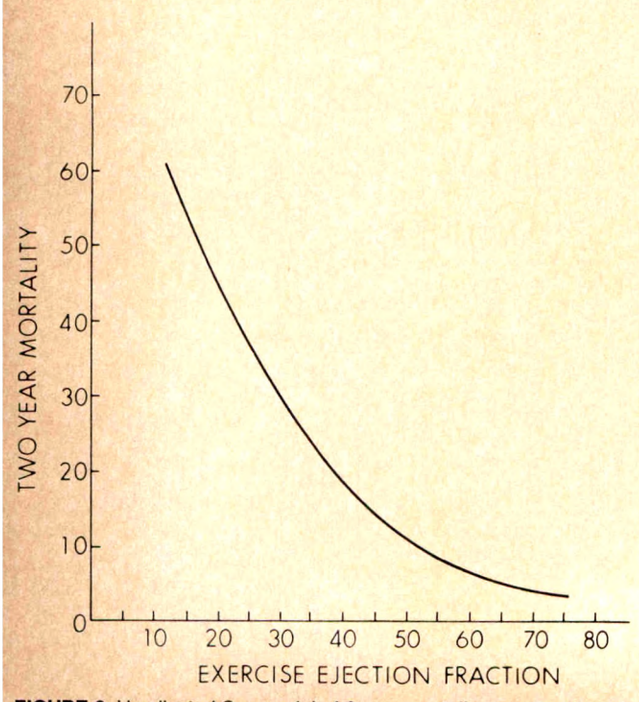

FIGURE 2. Unadjusted Cox model of 2-year mortality as a function of exercise ejection fraction.

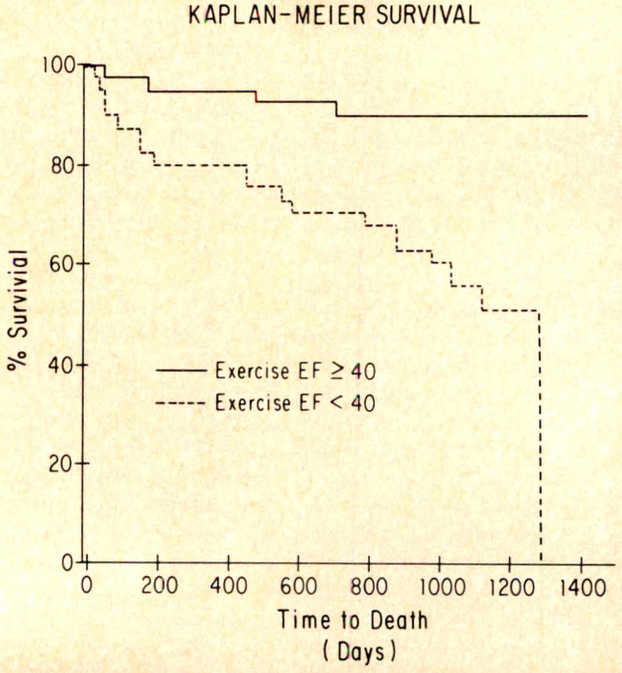

FIGURE 3. Life-table survival of patient population by exercise ejection fraction (EF). EF ≥ 40, n = 72; EF <40, n = 34.

showing a decrease in EF with exercise, but a low mortality. However, subjects with a severe reduction in rest EF often show either no change or an increase in EF during exercise, but a high mortality in the follow-up period. Thus, it is not inconsistent that the change in EF in the total population is not an independent predictor of mortality. Another factor that may influence the predictive ability of a change in EF during exercise is that a decrease in EF of 15% may have different significance when it decreases from 60% to 45% than when it decreases from 45% to 30%. In the latter case the compromise of LV performance produced by the combination of the prior infarction and exercise-induced ischemia is much greater than the former, and this combined effect is important prognostically. These observations are consistent with the hypothesis that the severity of LV dysfunction produced by the AMI is the most important predictor of survival, but that myocardial dysfunction caused by ischemia during exercise provides additional but not independent prognostic information concerning mortality.

While mortality appears to be related primarily to the severity of LV dysfunction and secondarily to the presence of residual myocardial ischemia, certain nonfatal ischemic events may be expected to correlate primarily with RNA indexes of ischemia such as the change in EF from rest to exercise and the occurrence of exercise-induced wall motion abnormalities. Neither the clinical variables nor the RNA parameters were predictive of recurrent infarction. Exercise-induced wall motion abnormality was the only RNA variable that was related to recurrent infarction, but this relation was of only borderline univariate significance.

Admission to the coronary care unit for unstable chest pain during the follow-up period was predicted by the clinical variables reflecting recurrent angina early in the postinfarction course. The absence of any relation between RNA variables and coronary care unit hospitalization for chest pain was surprising but may be due to the heterogeneous nature of clinical chest pain syndromes resulting in rehospitalization after infarction.

The relatively small number of patients undergoing CABG reflects the practice pattern at the Veterans Administration Medical Center during the period of the study; patients were selected for surgery primarily for angina refractory to medical therapy. RNA results were not reported and thus were not used as a criteria for surgical therapy. The RNA variables that were associated with this event were all indexes of exercise-induced ischemia. The change in EF from rest to exercise demonstrated the highest correlation with medically refractory angina. This variable was also correlated with the occurrence of exercise-induced ST depression, the only other prognostic variable in the data set other than the functional class for angina which might reflect residual jeopardized myocardium.

The results of this study are consistent with those of previous studies that suggest that rest EF as measured by RNA is related to subsequent mortality in the postinfarction population.[20–24] With the exception of the Multicenter Postinfarction Research Group, none of these studies had enough deaths to analyze the relation of EF to mortality in a detailed fashion. Most of these studies also analyzed EF as a dichotomous variable, which reduces its apparent prognostic significance.[25] The Multicenter Postinfarction Research Group Study[24] showed that mortality is related to rest EF in a continuous fashion. The present study demonstrates similar relations for both rest and exercise EF.

Corbett et al[26,27] analyzed the prognostic value of RNA after AMI in terms of combined cardiac events; mortality was not studied as a specific event. They observed that the change in EF from rest to exercise was the most important prognostic variable for combined cardiac events. Of the 74 combined cardiac events, 34 were limiting or refractory angina, 17 were persistent heart failure, 14 were recurrent AMI and 9 were deaths. They also reported that exercise EF correlated with 41 "major events," which included the deaths. However, it cannot be determined from the analysis which specific cardiac events were related to each RNA variable. DeWhurst and Muir[28] reported that an EF less than 35% or a decrease in EF with exercise greater than 5% occurred in 15 of the 17 patients who died in their series. They also found that the change in EF with exercise was associated specifically with subsequent postinfarction angina. In contrast to the present study, neither of the previous studies used rigorous statistical methods to determine the added value of RNA beyond clinical assessment.

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Prognostic Significance of Precordial ST-Segment Depression During Inferior Acute Myocardial Infarction

MARK A. HLATKY, MD, ROBERT M. CALIFF, MD, KERRY L. LEE, PhD, DAVID B. PRYOR, MD, GALEN S. WAGNER, MD, and ROBERT A. ROSATI, MD

To study the mechanism and prognostic importance of precordial ST-segment depression during inferior acute myocardial infarction, 162 patients admitted during 1969 through 1982 were identified. Patients with ST depression in leads V_1, V_2 and V_3 had significantly larger infarctions as assessed by a QRS scoring system. Hospital mortality was 4% (3 of 75) among patients without ST depression, and 13% (11 of 87) in patients with ST depression. The relation between the amount of ST depression and hospital mortality was significant ($p < 0.001$ by logistic regression), and remained significant ($p < 0.003$) after adjusting for other potentially prognostic factors. Among patients discharged from the hospital, the 5-year survival was 92% in those without precordial ST depression and 80% in those with precordial ST depression ($p = 0.058$ by the Cox model). Precordial ST-segment depression on the admission electrocardiogram during an inferior acute myocardial infarction indicates a larger infarction, predicts a higher hospital mortality and suggests a worse long-term prognosis after discharge.

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The significance of the precordial ST-segment depression that sometimes accompanies inferior acute myocardial infarction (AMI) remains controversial. This reciprocal change may result passively from inferior ST-segment elevation,[1] but several studies suggest that it may represent an active, primary process. In particular, it may indicate posterior epicardial injury and a larger area of jeopardized myocardium, consistent with the higher peak levels of creatine kinase and lower ejection fractions found in such patients.[2–6] Alternatively, this electrocardiographic (ECG) change may arise from anterior wall ischemia,[7] since some studies have found an association with left anterior descending stenosis,[8,9] although others have not.[4,10] Thus, precordial ST depression during inferior AMI may be a benign ECG finding of little clinical importance, or it may be a valuable marker of patients with increased risk.

The major goal of this study was to define the prognostic significance of the precordial ST-segment depression in the admission electrocardiogram of patients with inferior AMI. Since many other factors also affect prognosis after AMI, multivariable analyses were used to determine if precordial ST changes contribute independent information. The mechanism of precordial ST-segment changes was also investigated by identifying the location and estimating the extent of the acute infarct, as indicated by the QRS changes.

Methods

Since January 1969, data from all patients admitted to the Duke University cardiac care unit with AMI have been prospectively entered into a computer database, described in detail elsewhere.[11] Information on 52 clinical variables is recorded daily and stored. Patients have been followed after discharge at 6 months, at 1 year and annually thereafter.

All patients who met the following criteria were identified: a history of prolonged chest pain, characteristic changes in serum enzymes, and development of a Q wave 0.03 second or longer in lead aVF. Patients admitted to the cardiac care unit by interward or interhospital transfer were excluded. Patients with either history or ECG evidence of previous MI or ECG criteria for ventricular hypertrophy or bundle branch block were also excluded, as were those with ST elevation in leads V_1, V_2 or V_3. Patients with some ST-segment elevation in leads V_4, V_5 and V_6 associated with ST depression in V_1, V_2

From the Division of Cardiology, Department of Medicine, and the Division of Biometry, Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina. This work was supported by Research Grant HS 04873 from the National Center for Health Services Research, Rockville, Maryland; Research Grant HL 17670 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland; Training Grant LM 07003 and Grants LM 03373 and LM 00042 from the National Library of Medicine, Bethesda, Maryland; a grant from the Prudential Insurance Company of America, Newark, New Jersey; a grant from the Kaiser Family Foundation, Menlo Park, California; and a grant from the Andrew W. Mellon Foundation, New York, New York. Manuscript received May 14, 1984; revised manuscript received November 5, 1984, accepted November 6, 1984.

Address for reprints: Mark A. Hlatky, MD, P.O. Box 31265, Duke University Medical Center, Durham, North Carolina 27710.

and V_3 were accepted, however, if the amount of this ST elevation was less than that in inferior leads II, III and aVF, since this was considered indicative of inferoapical involvement.[12,13] Patients seen after June 1982 were excluded to ensure at least 1 year of follow-up for each patient.

Admission electrocardiograms were reviewed by cardiologists blinded to the follow-up information. ST-segment deviation was identified by a non-isoelectric J point. The amount and direction of any ST-segment deviation from the isoelectric baseline was measured at 0.08 second after the J point to the nearest 0.05 mV in all 12 leads. For purposes of analysis, the amount of ST-segment depression in leads V_1, V_2 and V_3 was summed.

Prognosis: The effect of precordial ST depression in V_1, V_2 and V_3 was examined for both short-term prognosis (hospital mortality) and long-term prognosis. To use all the information available, ST depression was used in statistical tests as a continuous variable rather than a categorical "present" or "absent." [14] For ease in describing the findings, however, the patients were divided into 2 groups. Patients in group 1 had less than 0.05 mV of ST depression in each of leads V_1, V_2 and V_3, and the remaining patients formed group 2.

The logistic regression model was used to test whether the sum of precordial ST-segment depression in leads V_1, V_2 and V_3 was predictive of hospital survival. Breslow's formulation[15] of the Cox proportional hazards model[16] was used to test whether the sum of precordial ST depression was predictive of long-term prognosis in hospital survivors. Initially, univariable analyses were performed. Subsequently, multivariable analyses were performed to test whether the sum of precordial ST-segment depression added significantly to the prognostic information provided by other factors.

The logistic regression model was also used to test whether the sum of precordial ST-segment depression in leads V_1, V_2 and V_3 was predictive of urgent complications during hospitalization. The occurrence of 1 or more of the following was considered an urgent complication[17]: ventricular tachycardia, ventricular fibrillation, persistent hypotension, Killip class III or IV, or reinfarction. Ventricular tachycardia was defined as 3 or more beats of ventricular origin at a rate of 100 beats/min or greater. Persistent hypotension was defined as a systolic blood pressure less than 90 mm Hg lasting for 1 hour or more.

Comparison of QRS changes: The pathogenesis of precordial ST depression was investigated by using the predischarge electrocardiogram to judge the size and extent of infarction by means of the QRS scoring system.[12,13] This scoring system consists of criteria regarding Q- or R-wave duration and amplitude ratios for each of 10 leads (I, II, aVL, aVF and V_1 through V_6). The accuracy of this method in predicting the size and location of myocardial necrosis has been validated.[12,13]

We hypothesized that (1) if precordial ST depression were the result of posterior injury, patients with this finding should show QRS changes of posterior infarction more frequently; and (2) if precordial ST depression were due to anterior subendocardial injury, patients with this finding should develop QRS changes of anterior infarction more frequently. To test the first hypothesis, the number of QRS points in leads V_1 and V_2 indicative of posterior wall damage developed by patients without precordial ST depression (group 1) was compared with the number of posterior wall QRS points developed by patients with precordial ST depression (group 2). Similarly, to test the second hypothesis, the number of anterior wall QRS points in leads V_1 through V_4 (development of Q waves or R-wave loss) developed by group 1 patients was compared to those developed by group 2 patients. Statistical significance was assessed by means of nonparametric 1-way analysis of variance (Kruskal-Wallis test).

Results

Prognosis: A total of 162 consecutive patients (120 men, 42 women) met entry criteria for the study. The median age was 58 years (range 33 to 89). Fourteen patients (8.6%) died in hospital and 32 more died from cardiovascular causes in the long-term follow-up period (median 4 years, range 1 to 10).

Hospital mortality was 4% (3 of 75) among patients with less than 0.05 mV of ST-segment depression in leads V_1, V_2 and V_3 (group 1), compared with 13% (11 of 87) in patients with at least 0.05 mV of ST depression in these leads (group 2). The sum of ST-segment depression was significantly related to hospital mortality when tested with the logistic model ($p < 0.001$). The risk of hospital death was greater with increasing amounts of ST-segment depression, without any evidence for a risk threshold.

The sum of precordial ST depression in leads V_1, V_2 and V_3 was significantly correlated with the sum of inferior ST elevation in leads II, III and aVF ($R^2 = 0.30$, mean squared error 3.8, $p < 0.0001$). While the sum of inferior ST elevation was also a predictor of hospital mortality, it was a weaker predictor than the amount of precordial ST depression. The sum of inferior ST elevation did not contribute prognostic information after adjusting for the sum of precordial ST depression in a stepwise logistic model.

Multivariable logistic regression was used to determine whether the prognostic information provided by precordial ST-segment depression regarding hospital mortality was independent of other potential prognostic factors. The prognostic importance of the sum of precordial ST-segment change remained significant ($p < 0.003$) after adjusting for the effects of the patient's age, sex, number of cardiac risk factors (hypertension, diabetes, smoking, hyperlipidemia, and family history of coronary disease), history of angina pectoris, history of cerebrovascular or peripheral vascular disease, admission chest roentgenographic findings, and initial Killip class. The year of hospital admission was not correlated with hospital mortality and its inclusion in the logistic regression model did not affect the significant relation of precordial ST depression with hospital mortality. The results were unchanged when the 9 patients with minor ST elevation in V_4, V_5 or V_6 were omitted.

Precordial ST depression was also significantly correlated with the likelihood of urgent complications during the initial hospitalization. Urgent complications (as defined in Methods) occurred in 24 of the 75 patients (32%) without precordial ST depression (group 1) and in 46 of the 87 patients (53%) with precordial ST depression (group 2). The sum of precordial ST depression was significantly related to the probability of developing urgent complications ($p = 0.002$ by the logistic model). This relation remained significant ($p = 0.0097$) after adjustment for the effects of the other clinical factors of potential prognostic value noted above.

The analysis of complications was repeated after excluding the patients who died during the hospitalization. Urgent, nonfatal complications occurred in 21 of the 72 patients (29%) without precordial ST depression and in 35 of the 76 patients (46%) with precordial ST-segment depression. The sum of precordial ST depression was significantly related to the probability of developing urgent, nonfatal complications ($p = 0.026$ by the logistic model). This relation was of borderline statistical significance ($p = 0.055$) after adjustment for other prognostic factors, probably because of the smaller sample size after exclusion of hospital deaths.

Survival after hospital discharge also differed depending on the sum of precordial ST-segment depression present on the admission ECG (Fig. 1). The survival at 1 year, 3 years and 5 years, calculated by the Kaplan-Meier method, was 96%, 94% and 92%, respectively, in group 1, and 89%, 86% and 80%, respectively, in group 2. The sum of precordial ST-segment change was a prognostic factor of borderline statistical significance, when tested univariately with the Cox model ($p = 0.058$). Multivariable analyses of long-term prognosis were not performed because of the borderline significance in the univariate analyses.

Comparison of QRS changes: The patients in groups 1 and 2 were compared to examine whether precordial ST-segment change was associated with a different extent or location of infarction by means of the QRS scoring system.[12,13] QRS scores could not be calculated in 3 of the 75 patients from group 1 and 4 of the 87 patients from group 2 because of development of bundle branch block, insertion of a pacemaker or lack of follow-up electrocardiograms. The median interval between the admission and predischarge electrocardiograms was 11 days.

Groups 1 and 2 had distinctly different patterns of infarction as judged by the QRS scoring system (Table I). Patients without ST depression (group 1) had significantly fewer overall QRS points ($p = 0.041$ by Kruskal-Wallis test), suggesting that the total area of infarction was smaller. Groups 1 and 2 were no different, however, in the number of QRS points developed in leads reflecting the inferior wall. If precordial ST depression were the result of anterior ischemia, a higher frequency of associated anterior infarction would be expected. There was, however, no significant difference in the amount of anterior QRS change between the 2 groups. Supporting the hypothesis that precordial ST depression indicates posterior epicardial injury was the observation that patients in group 2 had significantly greater amounts of posterior infarction ($p = 0.0012$). The amount of apical infarction was also significantly increased ($p = 0.0086$) when ST elevation in V_4, V_5 and V_6 accompanied ST depression in leads V_1, V_2 and V_3. These differences in the distribution of QRS points was not changed appreciably by excluding the 10 patients who had reinfarction before hospital discharge.

TABLE I Location and Mean QRS Points Relative to Precordial ST-Segment Depression

Leads	Precordial ST Depression: Absent (Group 1, n = 72)	Precordial ST Depression: Present (Group 2, n = 83)	p Value
Inferior (II, aVF)	3.6	3.6	0.880
Posterior (V_1,V_2)	0.5	1.0	0.001
Anterior (V_1–V_4)	0.3	0.4	0.701
Apical (V_5–V_6)	0.4	0.8	0.009
Lateral (I, aVL)	0.0	0.1	0.506
Total	4.8	5.9	0.041

Discussion

The major finding of this study was that patients with precordial ST-segment depression during an inferior AMI have a poorer prognosis. Patients with precordial ST depression had a hospital mortality rate of 13%, compared with 4% in the remaining patients. The risk of hospital death increased directly with the sum of ST depression, without evidence for a threshold, and the prognostic information it provided was independent of that provided by clinical factors and by the amount of inferior ST elevation. Finally, precordial ST depression was also predictive of urgent complications during the hospitalization among patients who survived.

Previous studies of precordial ST depression as a predictor of hospital mortality have yielded conflicting results. In the initial study by Shah et al,[2] hospital mortality was 21% (5 of 24) in patients with precordial ST depression, compared with 0% (0 of 20) in patients without ST depression. No other study has found as high a mortality rate in patients with precordial ST depression, and none had confirmed a significant difference in hospital mortality.[3–6,8,18]

The present investigation differs from previous studies in 2 important respects. First, most reported studies have included fewer than 50 patients, and none has included more than 110 patients with inferior AMI.

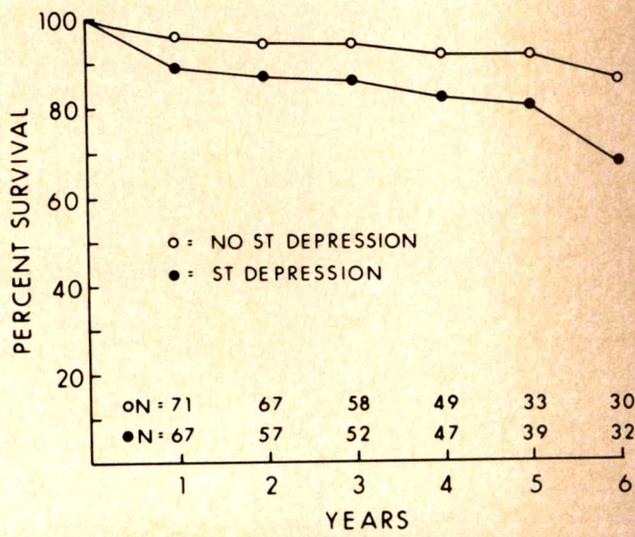

FIGURE 1. Cumulative survival of patients discharged from the hospital, according to the presence or absence of precordial ST-segment depression on the admission electrocardiogram.

The small sample sizes may have prevented previous studies from detecting real mortality differences. In most previous studies an insignificant trend toward higher hospital mortality related to precordial ST depression was present.[2,4–6,8,9,20] Second, the present study analyzed precordial ST depression as a continuous variable, rather than as simply "present" or "absent," to use all available information and increase statistical power.[14] Smaller sample sizes and insensitive statistical methods are particularly likely to mask clinically important differences in mortality.

Our results also suggest that the long-term prognosis of patients with precordial ST depression is worse than that of patients without this finding (Fig. 1). Among patients discharged from the hospital, the 5-year survival was 80% in patients with and 92% in patients without ST depression ($p = 0.058$ by Cox analysis of the entire survival curve). Previous studies have reported follow-up data after discharge from the hospital, but none has documented important differences in long-term mortality after discharge.[4–6,18,19] The largest study, that of Wasserman et al,[19] found equal mortality 3 years after inferior myocardial infarction whether or not precordial ST depression was present among 219 patients enrolled in the Aspirin Myocardial Infarction Study. However, patients in that study were highly selected and may not be representative of all patients with inferior infarction; all were Killip class I or II during hospitalization, and all had survived for at least 2 months after discharge before enrollment. The present study differs from previous studies by having more patients, or longer follow-up, or both.

Pathogenesis of ST depression: The mechanism of precordial ST depression remains controversial. ST depression might occur as a passive "reciprocal" phenomenon. We found, as others have, that the sum of ST elevation in the inferior leads II, III and aVF was correlated with the sum of precordial ST depression in leads V_1, V_2 and V_3. This correlation need not imply that precordial ST depression is a benign electrical phenomenon, however. Precordial ST depression was a stronger predictor of prognosis than inferior ST elevation, and the latter was not significant in the multivariable analysis.

Precordial ST depression may indicate a larger infarction. We examined this possibility by means of the QRS scoring system that correlates well with the location and extent of myocardial infarction.[12,13] Patients with precordial ST depression had larger total QRS scores, suggesting that they had larger infarctions (Table I). The size of the inferior infarct itself was similar, however, whether or not precordial ST change was present. Patients with ST depression in leads V_1, V_2 and V_3 had associated posterior wall and apical infarction significantly more often than patients without this ECG finding. In contrast, anterior and lateral infarctions were not associated with precordial ST depression. These observations suggest that precordial ST changes mark a group of patients with larger infarcts that often include the true posterior wall and apex.

The present study was not designed primarily to investigate the mechanism of precordial ST depression. Data from additional ECG leads, coronary angiography and ventriculography, which could have shed further light on the pathophysiologic mechanisms, were not available on most subjects. Our observations concerning the correlations between ST changes and QRS changes on the electrocardiogram are in broad accord with the findings of other investigators using more sophisticated techniques.

Most previous investigations have also found evidence of larger myocardial infarctions in patients with precordial ST depression. The peak creatine kinase level is usually higher in patients with precordial ST depression,[2–6] although this has not been a uniform finding.[17] Larger areas of inferior infarction in association with precordial ST-segment depression have also been disclosed by thallium-201 perfusion imaging.[4,6] Global left ventricular ejection fraction has usually been found to be lower in patients with precordial ST depression,[2–4,6] with 1 exception.[1] Several studies have examined regional wall motion abnormalities and correlated them with precordial ST change. These studies are difficult to compare because of variations in technique and nomenclature. Most found more extensive inferior wall motion abnormalities,[2,4,6] but disagree on the presence of other regional abnormalities. Some studies found no difference in wall motion outside the infarct zone,[1,4,6] while others found additional anteroseptal,[2] apical[3] or posterolateral[3] abnormalities.

Another potential cause of precordial ST depression is anterior ischemia due to concomitant disease of the left anterior descending coronary artery. In our study, evidence of associated anterior infarction was not more common in patients with precordial ST depression. Previous investigations disagree whether an association exists between left anterior descending disease and precordial ST depression, with some studies finding an association,[8,9] while others have not.[4,10] Scant evidence for anterior wall ischemia has been found with either thallium-201 perfusion imaging[4,6] or positron emission tomography.[20] The data are insufficient to establish anterior ischemia as the cause of most cases of precordial ST depression during inferior AMI, but cannot exclude it as a contributing factor in some cases.

Implications: Therapeutic decisions in patients during and after AMI depend on accurate assessment of prognosis, and precordial ST changes during inferior AMI may provide a valuable noninvasive method of classifying patients into high- and low-risk groups. Information from the admission electrocardiogram is available immediately, at no risk and little cost, in even the smallest community hospital. In high-risk patients, interventions aimed at reducing risk may be appropriate, while in low-risk patients, conservative therapy and rapid rehabilitation may be more suitable. Precordial ST changes mark patients at high risk of hospital complications or death, probably because of a larger area of infarction. Thrombolytic therapy is being investigated as a method of salvaging acutely jeopardized myocardium, and may be particularly indicated in patients with precordial ST depression during inferior AMI. While similar prognostic information may be

available from other methods (such as perfusion scintigraphy or radionuclide angiography), the immediate availability of such information from the admission electrocardiogram is an obvious advantage when rapid decisions must be made.

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Isosorbide Dinitrate Sublingual Therapy for Inferior Myocardial Infarction: Randomized Trial to Assess Infarct Size Limitation

PEDRO PABÓN OSUNA, MD, LUIS M. GARCÍA MORENO, MD, ANTONIO ARRIBAS JIMENEZ, MD, ANGEL SALA SÁNCHEZ-CASTILLO, MD, CÁNDIDO MARTÍN LUENGO, MD, JOSÉ SÁNCHEZ HERNÁNDEZ, MD, LUIS CASTAÑO BAZO, MD, MANUEL CASCÓN BUENO, MD, MAXIMILIANO DIEGO DOMINGUEZ, MD, and CLAUDIO LEDESMA GARCÍA, MD

To assess the potential of isosorbide dinitrate sublingual therapy for limiting myocardial infarct size, 41 patients with inferior acute myocardial infarction (AMI) were studied. Twenty patients were randomly assigned to the control group and 21 to the treatment group. Patients in the treatment group received 10 mg of isosorbide dinitrate every 2 hours for 72 hours. To estimate infarct size, QRS scoring, peak creatine kinase (CK) serum levels and CK curves were used. There were no significant differences between the 2 groups in maximal or cumulative activity of CK or QRS score (percent of left ventricle infarcted: 16% in the control group, 17% in the treatment group). In both groups the QRS score increased significantly by 13 hours after AMI, and the increase was highly significant by 19 to 23 hours. Thus, sublingual isosorbide dinitrate at the dosage given did not reduce infarct size in patients with inferior AMI.

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Isosorbide dinitrate, which is used for treatment of angina, has recently been used in the management of heart failure complicating acute myocardial infarction (AMI) and other heart diseases.[1–4] Isosorbide dinitrate is a vasodilator agent with a direct major effect on systemic veins and a mild but significant relaxing action on arterial smooth muscle.[2,4,5] The resultant reduction in intramyocardial tension and decrease in myocardial oxygen demand is probably the main mechanism in relieving angina and enhancing ventricular function in patients with heart failure. There is some evidence of dilating action on coronary arteries with improvement in collateral circulation and coronary blood flow in AMI.[6–8] Therefore, we undertook a prospective, randomized study to test the hypothesis that sublingual isosorbide dinitrate could significantly reduce infarct size. We selected 2 homogenous groups of patients with inferior AMI. The infarct size was estimated by analysis of changes in serum creatine kinase (CK) and by QRS scoring from standard 12-lead electrocardiograms (ECGs).

From the Servicio de Cardiologia del Hospital Clínico Universitario de Salamanca, Salamanca, Spain. Manuscript received July 12, 1984; revised manuscript received October 3, 1984, accepted October 8, 1984.

Address for reprints: Pedro Pabón Osuna, MD, Servicio de Cardiologia, Hospital Clinico Universitario, Paseo de San Vicente, 26, 37007 Salamanca, Spain.

Methods

Patients and criteria for inclusion: This study initially included 49 patients admitted to the coronary care unit who were suspected of having their first AMI, located in the inferior wall. Forty-one patients met all the inclusion criteria and 8 were excluded. The inclusion criteria were (1) typical chest pain, (2) epicardial injury pattern in leads II, III and aVF and pathologic Q waves in the same leads, (3) absence of electrical signs of right or left bundle branch block, anterior fascicular block and ventricular hypertrophy, (4) systolic blood pressure on admission greater than 100 mm Hg, (5) no history or electrical signs of previous AMI, and (6) no evidence of cardiac failure on admission.

QRS scoring system: In all patients a 12-lead ECG was recorded at enrollment and 2, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, 48 and 54 hours later. The QRS scoring system used was that developed by Selvester et al,[9] as modified by Wagner et

al[10] (Table I). All records were scored by 3 cardiologists independently without knowledge of the origin of the tracing. Interobserver agreement of the overall QRS score of every patient was assessed by analysis of variance. When significant differences among the 3 cardiologists were found, the QRS score mean value was taken.

Measurement of infarct size by enzymatic indexes: On admission and every 6 hours, blood samples were taken until 15 samples were collected, and the CK activity was measured in each sample. From the actual values, intermediate points (every 3 hours) were calculated by a method of curvilinear interpolation,[11] and expressed in IU/liter. The index chosen for biologic estimation of the infarct size was the cumulative activity of creatine kinase (CKr)[12]: $CKr = E(T) + Kd \int_0^t f(t)dt$, where E(T) = the actual concentration of enzyme, Kd = the constant of elimination and $\int_0^t f(t)dt$ = the area under the curve. Kd was obtained in each case from values of descending branch of the CK curve after transformation to a monoexponential regression equation.

Hemodynamic data: For 72 hours systolic and diastolic blood pressure (BP), central venous pressure and heart rate were measured every hour.

Treatment groups: On admission the patients were randomized to the control group or the treatment group. The patients admitted on Monday, Wednesday or Friday were assigned to control group and those admitted on Tuesday, Thursday or Saturday were included in treatment group. The control group included 20 patients who received no cardioactive drugs during the study. The treatment group included 21 patients, all of whom were treated with sublingual isosorbide dinitrate, 10 mg every 2 hours for 72 hours. The first dose was always 10 mg, but if at the time of administration of subsequent doses the systolic BP was less than 100 mm Hg, the dose was reduced to 5 mg. The groups were comparable with respect to QRS score of the first ECG, CK values at entry, sex distribution and age.

Statistical analysis: *QRS scoring:* the differences between the QRS scores of both groups were assessed by Kruskal-Wallis test.[13] The differences among QRS scores in each group were determined by the Friedmann test and Wilcoxon-Wilcox test, using the Pearson and Hartley tables.[14] To compare the QRS changes in both groups curves of repeated measures of the QRS score over time were constructed.

Enzymatic analysis: We studied the maximal activity of CK (CKp), time to peak of CK (Tck), CKr and Kd. A Student *t* test was applied to differences between control and treatment groups. To study the differences in Tck between both groups, a Mann-Whitney U test was applied. The analysis of correlation among enzymatic variables was assessed using a multilinear regression test.[15] To study the correlation between QRS score and enzymatic variables, a Spearmann test was used.[16]

Hemodynamic indexes: Systolic and diastolic BP, central venous pressure and heart rate were recorded. To assess the differences between the initial values of each variable and its average value over 48 hours, the Student *t* test for paired samples was used. The significance of the differences between both groups was studied by the Student *t* test for small and independent samples. In the treatment group the individual values of BP measured before every dose of isosorbide dinitrate were compared with the values 1 hour after sublingual administration of the drug; a Student *t* test for paired samples was used for analysis.

Results

QRS scoring system: In the control and treatment groups the mean evolution time between the onset of symptoms and the admission of the patients to the coronary care unit was 3 hours (range 0 to 9). On admission the mean QRS score was 3 points in both groups. The maximal values were 6.6 points in control group and 6.9 points in treatment group (difference not significant [NS]). The Kruskal-Wallis test showed no statistically significant differences in QRS score between the groups throughout the study period. Analysis of the QRS score, estimated by Wilcoxon test showed that the increase of QRS score from the first ECG was significantly different at 13 hours of evolution of AMI ($p < 0.05$) and was highly significant ($p < 0.0001$) at 19 to 23 hours. From this time the QRS score continued to increase, but very slowly, so that the trend curves showed a marked flattening. The statistical significance of the differences from the first ECG increased over the study period. Significant differences between the QRS score at 23 hours and subsequent records were not

TABLE I Simplified QRS Scoring System

Lead	Duration (ms)	Amplitude Ratios	Maximal Points
I	Q ≥ 30	(1) R/Q ≤ 1 (1)	2
II	Q ≥ 40	(2)	
	Q ≥ 30	(1)	2
aVL	Q ≥ 30	(1) R/Q ≤ 1 (1)	2
aVF	Q ≥ 50	(3) R/Q ≤ 1 (2)	
	Q ≥ 40	(2)	
	Q ≥ 30	(1) R/Q ≤ 2 (1)	5
V_1	Any Q	(1)	
	R ≥ 50	(2)	
	R ≥ 40	(1) R/S ≥ 1 (1)	4
V_2	Any Q or R ≤ 10	(1)	
	R ≥ 60	(2)	
	R ≥ 50	(1) R/S ≥ 1.5 (1)	4
V_3	Any Q or R ≥ 20	(1)	1
V_4	Q ≥ 20	(1) R/Q or R/R ≤ 0.5 (2)	
		R/Q or R/S ≤ 1 (1)	3
V_5	Q ≥ 30	(1) R/Q or R/S ≤ 1 (2)	
		R/Q or R/S ≤ 2 (1)	3
V_6	Q ≥ 30	(1) R/Q or R/S ≤ 1 (2)	
		R/Q or R/S ≤ 3 (1)	3

Numbers in parentheses = points of the QRS score.

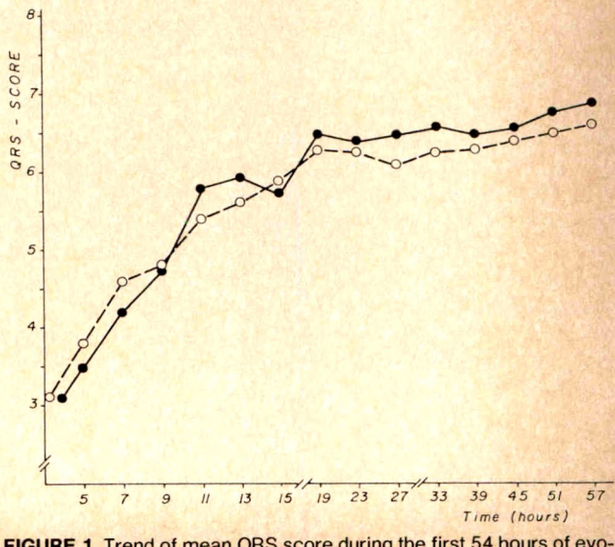

FIGURE 1. Trend of mean QRS score during the first 54 hours of evolution of myocardial infarction. Superimposition of curves in control (**open circles**) and treatment (**solid circles**) groups. Time indicates mean time from onset of symptoms.

TABLE II Enzymatic Values in Control and Treatment Groups

Parameters	Control Group	Treatment Group
CKp (IU/liter)	1,185 ± 493	1,142 ± 449*
CKr (Hr × IU/liter)	1,646 ± 676	1,734 ± 824*
Kd (hour^{-1})	0.042 ± 0.007	0.044 ± 0.001*
Tck (hours)	20 ± 5	21 ± 7*

* No significant differences between groups.
CKp = peak creatine kinase level; CKr = accumulated CK activity; Kd = enzyme disappearance rate; Tck = time to peak CK.

found. Figure 1 shows the similarity of QRS scores in both groups and the flattening of the curves at about midpoint.

Enzymatic estimation of infarct size: On admission all patients were in the upslope of their enzyme curves; the initial values of CK were 128 ± 45 and 138 ± 52 IU/liter in the control and the treatment groups, respectively. The mean values of CKp were 1,185 ± 493 IU/liter in the control group and 1,142 ± 449 IU/liter in the treatment group. The CKr mean values were 1,646 hours × IU/liter in the control group and 1,734 hours × IU/liter in the treatment group. The respective values of Kd were 0.042 and 0.044 hours^{-1}, whereas the Tck reached 20 ± 5 hours in the control group and 22 ± 4 hours in the treatment group. The differences between the mean values of each measurement in the 2 groups were not statistically significant (Table II). In the control group a good correlation between CKp and CKr ($r = 0.97$) was found, although the correlation was better ($r = 0.99$) when Tck and Kd were included. Similar results were found in the treatment group. Analysis of correlation among the 4 enzymatic variables yielded very high coefficients of determination, showing that each variable can be expressed as a function of the others by a multiregression equation.

Correlation between QRS score and enzymatic variables: The analysis of correlation between QRS score and enzyme levels yielded the following results: (1) The Spearmann test showed no correlation between peak QRS score and CKp or CKr. (2) The Tck did not show correlation with the time to peak QRS score. (3) When QRS scores were individually measured at the Tck, a slight but significant correlation was found between them and the CKp ($r = 0.48$ and 0.49 in control and treatment groups, respectively, $p < 0.05$).

Hemodynamic features (Table III): The average systolic BP at entry into the study was 125 ± 18 mm Hg in the control group and 135 ± 23 mm Hg in the treatment group (NS). The diastolic BP was 78 mm Hg in the control group and 87 mm Hg in the treatment group (NS). In both groups the average BP in the first 48 hours of evolution of the AMI was significantly lower than the value at entry. The decrease in BP in the treatment group (16%, $p < 0.0001$) was larger than that in the control group (7%, $p < 0.05$). In the treated patients the individual values of BP before every dose of isosorbide dinitrate were compared with the values 1 hour after the intake of the drug. The average systolic BP values were 125 ± 12 mm Hg before treatment and 110 ± 10 mm Hg 1 hour after sublingual administration of isosorbide dinitrate (11% decrease, $p < 0.0001$). The diastolic BP decreased from 82 ± 10 mm Hg before the intake of the drug to 75 ± 10 mm Hg 1 hour later (8.5% decrease, $p < 0.0005$). At entry into the study the mean central venous pressure was 7 mm Hg in both groups and the heart rate was 74 ± 11 and 73 ± 15 beats/min in the control and treatment groups, respectively (NS). The changes in these measurements during the evolution of AMI were not statistically significant.

TABLE III Mean (± Standard Deviation) Hemodynamic Values on Admission and During the 48 Hours of Evolution of Myocardial Infarction

Measurements	Time 0	Evolution	% Decrease
	Control Group		
SBP (mm Hg)	125 ± 18	114 ± 11	9%*
DBP (mm Hg)	78 ± 10	72 ± 6.5	8%‡
CVP (mm Hg)	7 ± 3	8 ± 2	11%‡
HR (beats/min)	74 ± 11	74 ± 10	0%‡
	Treatment Group		
SBP (mm Hg)	135 ± 23	114 ± 11	16%†
DBP (mm Hg)	87 ± 17	73 ± 7	16%†
CVP (mm Hg)	7 ± 3	7 ± 2	4%‡
HR (beats/min)	73 ± 15	74 ± 14	2%‡

* $p < 0.05$; † $p < 0.0001$; ‡ no significant differences.
CPV = central venous pressure; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

Discussion

Loss of myocardial mass is the most frequent cause of pump failure and the major determinant of short- and long-term prognosis in patients with AMI.[17,18] Over the last 10 years, attempts to limit infarct size have gained a prominent place in research of therapy during AMI. Preliminary reports have shown that the intravenous nitroglycerin reduces the enzymatically estimated infarct size.[19–21] Nevertheless, it is not clear whether nitrates administered orally, sublingually or topically may be useful for this purpose. Like nitroglycerin, isosorbide dinitrate may have the potential of reducing infarct size, because it reduces the myocardial oxygen demand by a decrease in the preload and afterload. To test this hypothesis, we studied the effects of isosorbide dinitrate in patients with inferior AMI, selecting the QRS scoring system and changes in serum CK as index to estimate infarct size.

QRS scoring system: To estimate the infarct size, analysis of changes in serum CK,[12] nuclear ventriculography[22] and electrocardiographic changes[23] have been used. Selvester et al[9] reported a method based on the accumulation of points obtained from Q-wave duration and R/Q and R/S amplitude ratio on standard 12-lead ECG (QRS scoring system). Wagner et al[10] developed a simplified version of this method, testing only quantitative criteria and comprising 37 criteria with a total of 29 points. Correlation between QRS scoring and percent of infarcted left ventricle showed that 1 point of the score represents infarction of about 3.5% of left ventricle in an anterior infarct[24] and 2.5% in an inferior infarct.[25] In our study the highest QRS score achieved was 6.6 points in the control group (percent of left

ventricle infarcted = 16.5%) and 6.9 points in the treatment group (percent of infarcted left ventricle = 17%); this difference was not statistically significant. Also, the serial ECG showed a similar evolutionary trend in the 2 groups. Our results suggest, therefore, that isosorbide dinitrate did not affect the evolution of AMI during the first 54 hours of the acute coronary event. In our patients the QRS score showed a rapid increase in the first 24 hours and a very slow increase during the remainder of the follow-up period; similar increases in QRS score have been reported by Anderson et al[26] between the second and third day of the inferior infarcts. A good correlation (r = 0.74) between QRS score and anatomically estimated infarct size has been proved,[25] suggesting that changes in the QRS score are related to changes in the infarct size. Nevertheless, other mechanisms have been postulated. An increase of extravascular fluid in the infarcted myocardium, which could explain QRS changes, has been experimentally proved.[27] Hutchins and Bulkley[28] have reported the "infarct expansion" mechanism, in which the infarcted myocardial wall stretches and thins, increasing the proportion of infarcted myocardium exposed to surface electrodes. Nevertheless, neither mechanism explains the results of our trial, because both have been observed from the fourth day of the onset of infarction, and our patients were studied within the first 2 days. Therefore, in our trial, the increase in QRS score is probably related to an increase of the necrosis area. Although the causes of late extension of the infarct are not clear, Anderson et al[26] suggested that the blood flow in the border zone is reduced, small hemodynamic changes could result in an increase in the extent of the infarct. Anderson et al[26] suggested that interventions initiated later than the first few hours after the onset of symptoms may have more potential for limiting infarct size than previously considered. The results of our trial suggest that the infarction process in the left ventricle progresses the most within the first 24 hours of the AMI; after that period, progression of the infarct is very small. Because of this, attempts to limit the infarct size should be instituted within the first 24 hours after the onset of AMI.

Enzymatic estimation of the infarct size: Statistical analysis yielded no significant differences in mean enzymatic values between the control and treatment groups. The CK curves were used to assess the effects of therapy aimed at limiting infarct size. Although several studies indicated a good correlation between CKr and anatomically estimated infarct size,[29] some shortcomings of the method should be noted. Essentially, CK kinetics are based on a 2-compartment system, whereas the curves of the enzyme are based on a 1-compartment mathematical model; consequently, the Kd can be underestimated, leading to miscalculation of CKr.[30] However, the good correlation between CKp and CKr reported previously[31] and found in the present trial suggests that the CKp can be taken as an alternative in infarct size estimation. In our study, 6-hour sample intervals for CK analysis were chosen because it has been suggested that this time should encompass the CKp.[31] The reperfusion of an occluded coronary artery produces an important and fast enzymatic release, which could suggest a large infarct when in fact it is associated with small necrosis[32]; although isosorbide dinitrate is not a thrombolytic agent, the possibility of a spontaneous revascularization in some patients cannot be excluded in our study. Another factor reducing the sensitivity of the enzymatic method in inferior infarct is the association of right and left ventricular necrosis.[33] No patients of the present study showed clinical or electrical signs of right ventricular involvement. Finally, some pharmacologic interventions can disturb the fractional disappearance of CK,[34,35] although we do not know whether isosorbide dinitrate has some effect in this regard.

Correlation between QRS score and enzymatic analysis: In the present study no correlation was found between the peak QRS score and CKp or between the time to peak QRS score and Tck. However, when the QRS score was taken at the Tck, a mild but significant correlation was found. These signs suggest that there could exist a delay between QRS changes and enzymatic changes. Seino et al[36] reported good correlation between enzymatically estimated infarct size and QRS score on the seventh day after the onset of AMI, but not the third day. We suggest other explanations for the relatively low correlation between QRS score and enzyme levels. Initially, some studies showed that the pathologic Q waves can be masked by the current injury and unmasked when the current injury disappears[37,38]; we do not know whether this mechanism has had some influence on the results of our study because we have not analyzed the relation between the ST-segment resolution and QRS changes. On the other hand, if "infarct expansion" is present, the infarct estimated by QRS score can seem larger than that measured by enzyme levels. Finally, if the reperfusion of an occluded coronary artery occurs, the enzyme-estimated infarct size could seem larger than studied by QRS changes.

Hemodynamic aspects: In control and treatment groups, the average BP during the follow-up period was significantly lower than that at entry into the study, perhaps related to adrenergic tone during the acute event. Nevertheless, the decrease in BP was more prominent in the treatment group ($p < 0.0001$) than in the control group ($p < 0.05$). Additionally, in the treated patients, an average decrease of 11% in systolic BP ($p < 0.0001$) and 8.5% in diastolic BP ($p < 0.0005$) was found after every dose of isosorbide dinitrate. Similar results have been reported by others.[2,4,5] In contrast, in the control group, the BP did not change significantly during the follow-up period. Consequently, although the complete right-sided cardiac catheterization was not performed, our results provide indirect evidence for drug effects.

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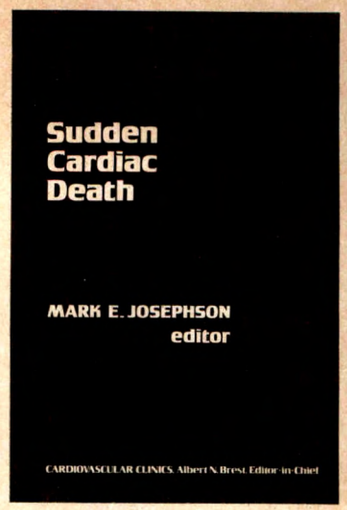

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TABLETS

INDICATIONS

Essential hypertension, alone or as an adjunct.

CONTRAINDICATIONS

Hypersensitivity to hydralazine; coronary artery disease; and mitral valvular rheumatic heart disease.

WARNINGS

Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary.

Complete [illegible] antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms.

A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Use MAO inhibitors with caution in patients receiving hydralazine.

When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and Apresoline (hydralazine hydrochloride) are used concomitantly.

Usage in Pregnancy

Animal studies indicate that hydralazine is teratogenic in mice, possibly in rabbits, and not in rats. Teratogenic effects observed were cleft palate and clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should not be used during pregnancy unless the expected benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Myocardial stimulation produced by Apresoline can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore be used with caution in patients with suspected coronary artery disease.

The "hyperdynamic" circulation caused by Apresoline may accentuate specific cardiovascular inadequacies. An example is that Apresoline may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from Apresoline, but is less common than with ganglionic blocking agents. Use with caution in patients with cerebral vascular accidents.

In hypertensive patients with normal kidneys who are treated with Apresoline, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances improve

According to a recent study appearing in the British Medical Journal[1]

The most "acceptable" antihypertensive to use with a beta blocker and a diuretic is...*

...function has been noted where control values ...e below normal prior to Apresoline administra... ...n. However, as with any antihypertensive agent, ...esoline should be used with caution in patients ...h advanced renal damage.

...ipheral neuritis, evidenced by paresthesias, ...nbness, and tingling, has been observed. Pub... ...ed evidence suggests an antipyridoxine effect ...f the addition of pyridoxine to the regimen if ...mptoms develop.

...od dyscrasias, consisting of reduction in hemo... ...bin and red cell count, leukopenia, agranulocy... ...is, and purpura, have been reported. If such ...normalities develop, discontinue therapy. Periodic ...od counts are advised during prolonged therapy.

...e Apresoline tablets (10 and 100 mg) contain ...&C Yellow No. 5 (tartrazine) which may cause ...rgic-type reactions (including bronchial asthma) ...ertain susceptible individuals. Although the over... ...ncidence of FD&C Yellow No. 5 (tartrazine) ...sitivity in the general population is low, it is ...quently seen in patients who also have aspirin ...ersensitivity.

...VERSE REACTIONS

...erse reactions with Apresoline are usually revers... ...when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.

Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris.

Less frequent: Nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE AND ADMINISTRATION

Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective levels.

The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.

In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.

HOW SUPPLIED

Tablets, 10 mg (pale yellow, dry-coated); bottles of 100 and 1000.

Tablets, 25 mg (deep blue, dry-coated) and 50 mg (light blue, dry-coated); bottles of 100, 500, 1000 and Accu-Pak® blister units of 100.

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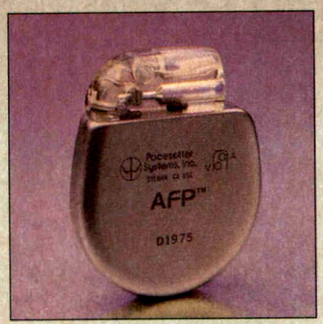

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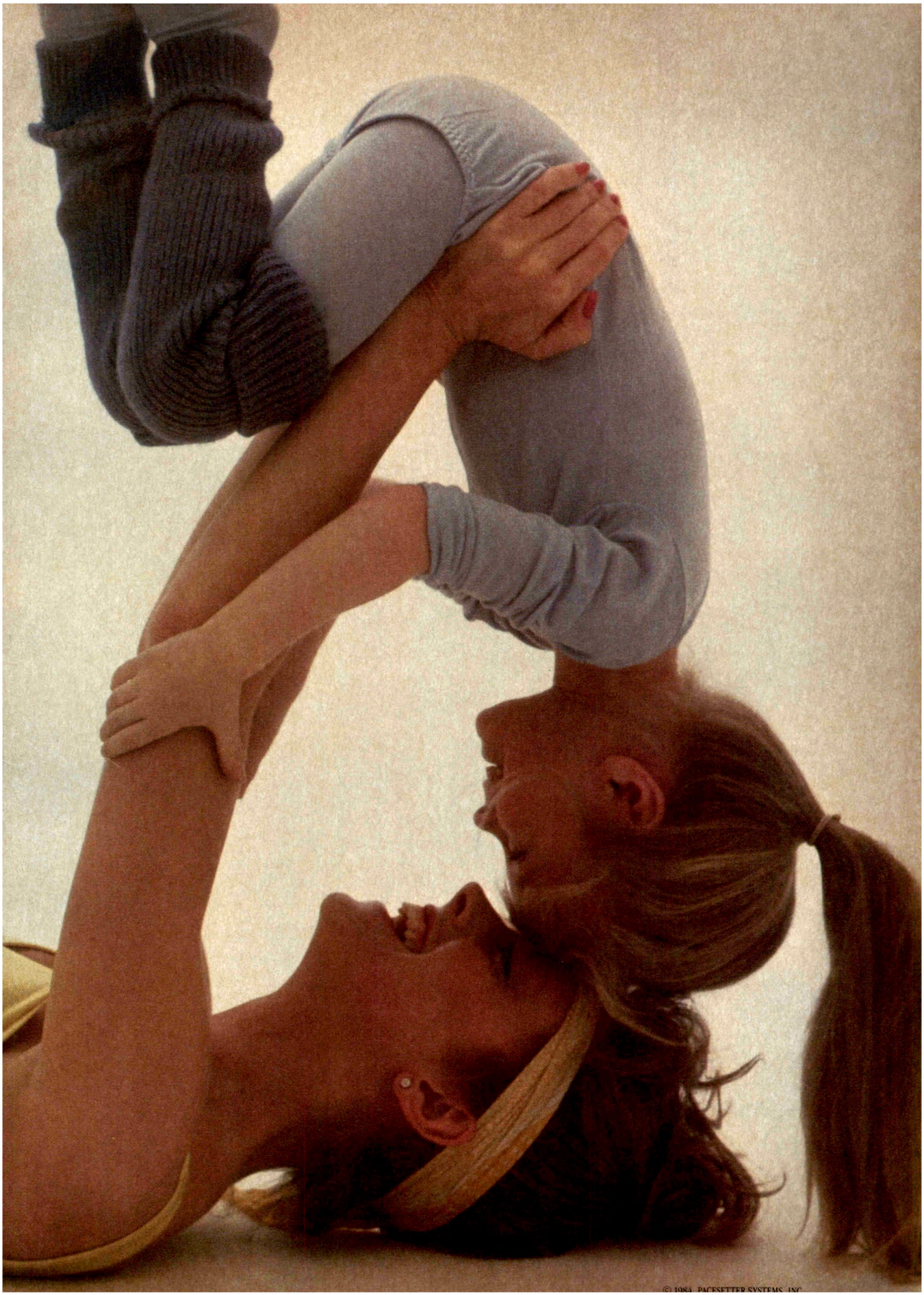
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The stairs seem steeper today

Most days she can climb the stairs with no difficulty. But today she was less than half-way up when an angina attack stopped her.

That's the unpredictability of MIXED ANGINA—vasoconstriction coexisting with fixed coronary lesion, to produce a critical reduction of myocardial blood flow.

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As a result, PROCARDIA can significantly reduce your patient's angina attack rate and need for nitroglycerin.[1]

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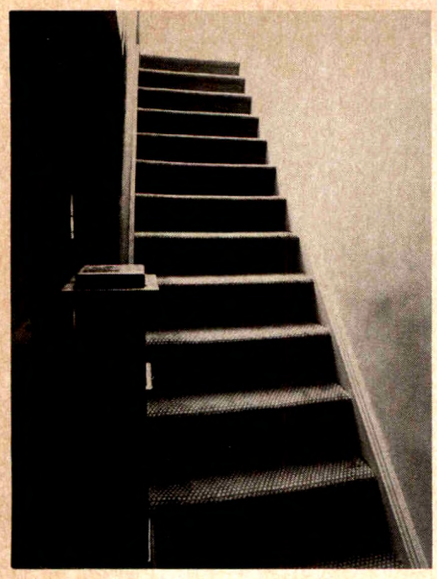

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PRIMARY PROTECTION IN MIXED ANGINA

Usual Effective Dosage: 30 to 60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level a a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and th patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration c severity of angina on starting PROCARDIA or at the time of dosage increases.

A Favorable Safety Profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

Reference:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 106:644-652, 1983.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestiv heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricula dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phos phatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA (nifedipine) therapy is uncertai in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symp toms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have bee reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregatio and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has bee demonstrated.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 pa tients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blockin agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination ma increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlle studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteer The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with corc nary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which d goxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, an discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin ar ticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80% and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg p day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently recei ing cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two yea and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a do approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mi and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used durir pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edem nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5 palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramp nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramp flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balanc dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, pu pura, allergic hepatitis, gingival hyperplasia, and erythromelalgia. Very rarely, introduction of PROCARDIA therapy w associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of t disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardi infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular a rhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CA SULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperatu 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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INDICATIONS AND USAGE
Visken® (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/ kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

	Total (Volunteered and Elicited)		
Body System/ Adverse Reaction	Visken (pindolol) (N = 322) %	Active controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

* Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and non-thrombocytopenic purpura.

Gastrointenstinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥ 80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 5 mg b.i.d. alone or in combination with other antihypertensive agents. An antihypertensive response usually occurs within the first week of treatment. Maximal response, however, may take as long as or occasionally longer than two weeks. If a satisfactory reduction in blood pressure does not occur within 3-4 weeks, the dose may be adjusted in increments of 10 mg per day at these intervals up to a maximum of 60 mg per day.

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[VIS-Z3 6/15/83]

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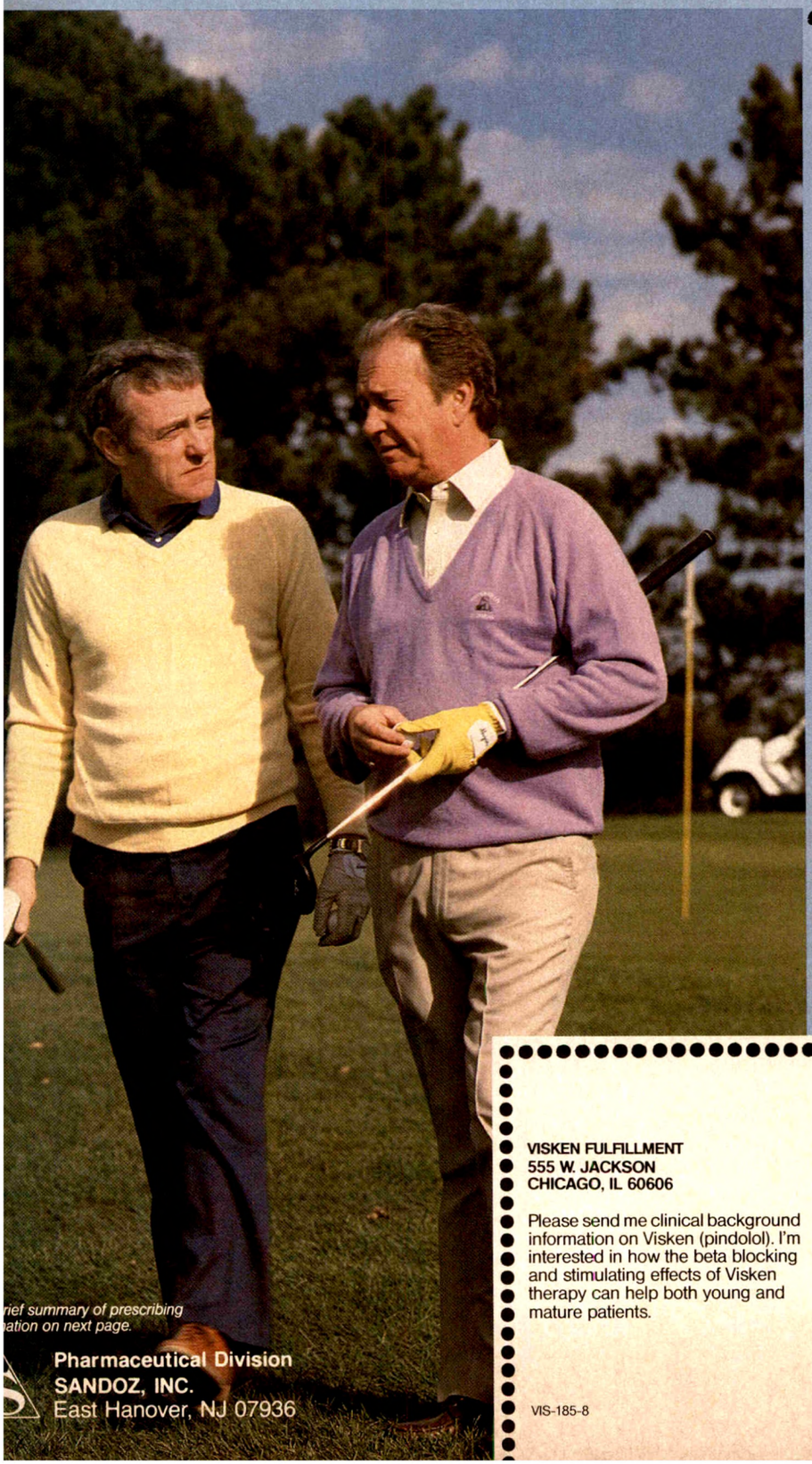

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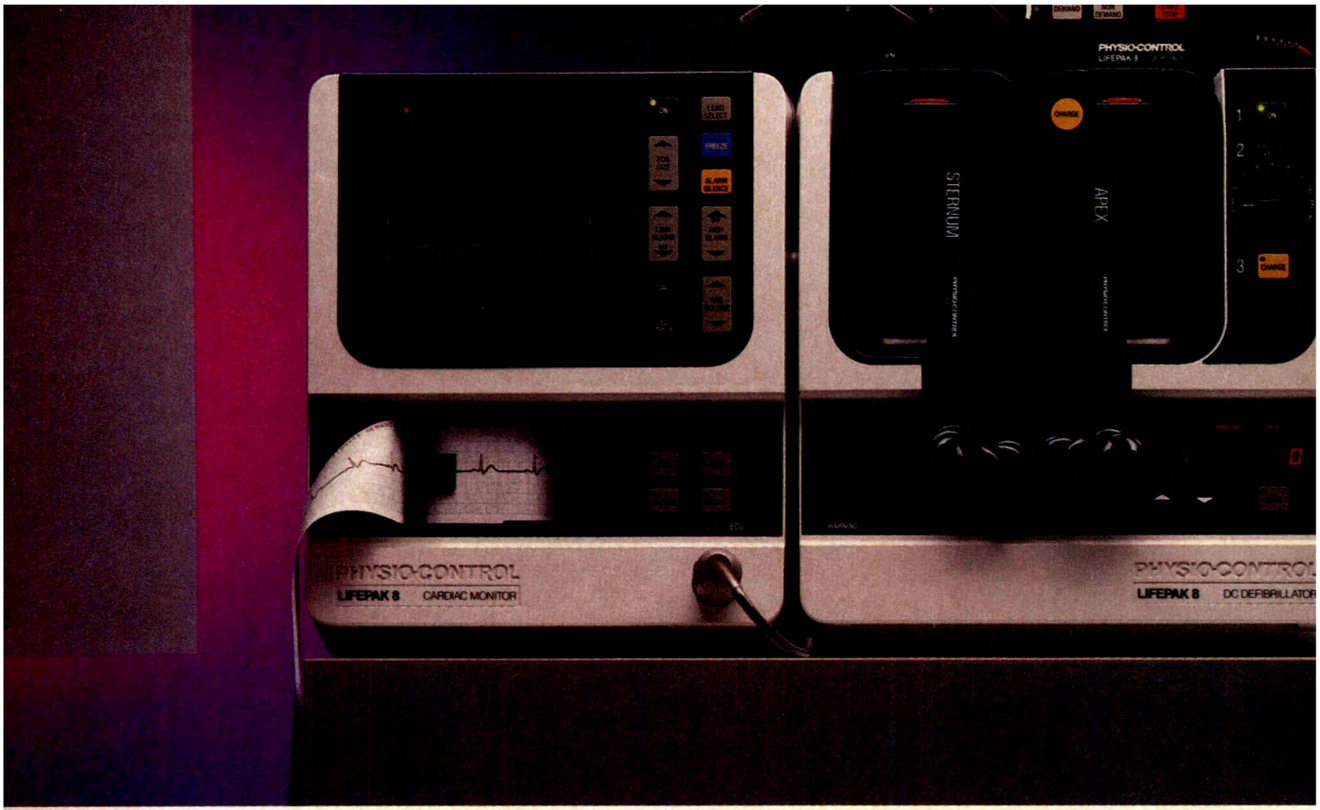

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Frequency of Pericardial Effusion as Determined by M-Mode Echocardiography in Acute Myocardial Infarction

KERRY KAPLAN, MD, RICHARD DAVISON, MD, MICHELE PARKER, RN, MS, JEAN PRZYBYLEK, RN, MS, AMY LIGHT, BS, DENNIS BRESNAHAN, MD, HILLEL RIBNER, MD, and JAMES V. TALANO, MD

A pericardial friction rub occurs in 6 to 16% of patients after acute myocardial infarction (AMI), but the incidence of pericardial effusion (PE) is not known. M-mode echocardiography was done 1, 3 and 5 days after AMI in 43 consecutive patients admitted within 24 hours of AMI, and PE was detected in 16 (37%). The PE was small in 7 patients, moderate in 6 and large in 3. A pericardial friction rub developed in 8 (19%), of whom only 4 had PE. Pleuritic chest pain diminished by sitting up and relieved by antiinflammatory agents developed in 12 (28%), of whom only 5 had PE. The peak creatine kinase level was significantly higher in patients with PE (1,769 ± 1,003 U) than in those without (1,181 ± 838 units). More patients with PE were in Killip classification II, III or IV (11 of 16 [69%] vs 9 of 27 [33%]). The presence of PE was not associated with age, site of AMI, development of Q waves, use of heparin or previous AMI. In conclusion, PE as detected by M-mode echocardiography is frequently present after AMI, and its presence is not closely associated with the occurrence of a pericardial friction rub or typical pericardial pain.

(Am J Cardiol 1985;55:335–337)

A pericardial friction rub occurs in 6 to 16% of patients after an acute myocardial infarction (AMI).[1–6] These patients frequently have pleuritic chest pain, lessened by sitting up and relieved by antiinflammatory agents; however, the incidence of pericardial effusion (PE) is unknown. The objective of this study is to determine the incidence of echocardiographically detected PE after AMI.

Methods

Patient selection: Patients admitted to the coronary care unit at Northwestern Memorial Hospital within 24 hours of a suspected AMI were considered eligible for inclusion in this study if they did not have a concomitant condition associated with PE or pericarditis. One hundred sixty-two patients were screened for inclusion in the study and 86 were excluded for the following reasons: AMI (28 patients) or cardiac surgery (7) within 6 months, cardiogenic shock (5), chronic renal failure (with BUN >50 mg/dl, creatine >4 mg/dl) (12), metastatic disease (8), rheumatoid arthritis (2), systemic lupus erythematosus (1), progressive systemic sclerosis (1), ankylosing spondylitis (1), chronic congestive heart failure with pleural effusions (9), or refusal of patient (10) or attending (2) to give consent. Thirty-one of the 86 excluded patients were later diagnosed as having AMI.

Seventy-six patients consented to the study. In 3 patients a technically satisfactory echocardiogram could not be obtained on the first day, and these patients were excluded from further analysis. Thirty patients had initial echocardiograms performed and were later found not to have had AMI. This report is based on the remaining 43 patients who had serial M-mode echocardiography after an AMI.

Methods: M-mode echocardiography was performed with either a Smith Kline Ekoline or Irex System II ultrasonoscope with a 2.25-MHz transducer. Standard technique was used with the transducer placed in the parasternal position. A switch-gain ("damping") mechanism was used to evaluate the pericardial space.

The initial echocardiogram was performed within 24 hours of admission for a suspected AMI; echocardiograms were repeated from the same chest position on the third and fifth day. In patients who had PE, echocardiograms were repeated 2 times per week until the effusion resolved or the patient was discharged from the hospital.

Clinical evaluation: AMI was diagnosed by the association of a compatible clinical presentation with either creatine kinase-MB ≥5% on 2 determinations or a positive technetium pyrophosphate myocardial scan. Myocardial infarctions were then classified as either Q wave with the appearance of 2 or

From the Section of Cardiology, Department of Medicine, Northwestern University Medical School and Department of Nursing, Northwestern Memorial Hospital, Chicago, Illinois. Manuscript received June 14, 1984; revised manuscript received November 5, 1984, accepted November 6, 1984.

Address for reprints: Kerry Kaplan, MD, Suite 628, 251 East Chicago Avenue, Chicago, Illinois 60611.

TABLE I Patient Characteristics

	Total Pts	With PE	Without PE
No. of pts	43	16 (37%)	27 (63%)
Age (yr)	58 ± 10	60 ± 11	57 ± 9
Sex			
Male	27	6†	21
Female	16	10†	6
Actual/ideal weight‡	1.21 ± 23	1.27 ± .16	1.18 ± .25
Site			
Anterior	14	4	10
Inferior	23	7	16
Indeterminate	6	5	1
Type			
Q	33	12	21
Non-Q	7	2	5
Peak CK	1,405 ± 938	1,769 ± 1,003*	1,181 ± 838
Peak LDH	738 ± 441	822 ± 401	687 ± 463
Peak SGOT	217 ± 160	238 ± 159	205 ± 163
Maximum Killip class I	23	5†	18
Maximum Killip class II, III, IV	20	11†	9
Heparin	14	6	8
Previous myocardial infarction	12	4	8
Clinical pericarditis	12	5	7
Pericardial friction rub	8	4	4

* $p < 0.05$ for comparison of mean values.
† $p < 0.05$ for comparison of ratios between groups.
‡ Ideal weight for sex, height and medium type frame.[9]
PE = pericardial effusion.

more Q waves of at least 0.04 second or non-Q wave with the appearance of 1 mm or more of ST depression or symmetric T-wave inversions persisting for 3 days or longer.

A clinical diagnosis of pericarditis was made either by auscultation of a pericardial friction rub or by the presence of classic pericardial chest pain, lessened by sitting up and relieved by antiinflammatory agents. Patients were evaluated at least twice daily by a cardiologist. Special attention was directed to the detection of pericardial friction rubs and evaluation of chest pain for characteristics suggestive of pericarditis. This study was approved by the Northwestern University Institutional Review Board and the Northwestern Memorial Hospital Research Committee.

Echocardiographic evaluation: Presence of PE was assessed using the method described by Horowitz et al.[7] The presence of a C2 or D pattern was considered indicative of PE. Two echocardiographers independently analyzed the first 3 echocardiograms in each series without knowledge of the patient's identity or clinical course. On the initial analysis there was disagreement on the presence of PE in 3 patients; these differences were resolved by a concurrent review of these echocardiograms. The amount of PE was estimated as small, moderate or large using standard techniques.[8]

Data analysis: Differences in proportions of categorical variables were tested for significance by the chi-square analysis with Yates continuity correction. For continuous variables, differences were tested for significance by the *t* test for unpaired data or the Wilcoxon rank-sum test. Statistical significance was considered at the $p < 0.05$ level. Values are expressed as mean ± standard deviation.

Results

Patient characteristics (Table I): Forty-three patients were entered into the study. The average age was 58 ± 10 years. Thirty-three of the patients had Q-wave AMI. Seven patients had non-Q-wave AMI. In 3 patients the presence of an intraventricular conduction disturbance made classification unreliable. The site of AMI was anterior in 14 patients, inferior in 23 and indeterminate in 6 (3 with conduction disturbances and 3 with lateral T-wave changes). Fourteen patients received subcutaneous heparin, 5,000 U twice daily. Twelve patients had had a previous AMI. Twelve patients (28%) had typical pericardial chest pain; in 8 of these 12 patients a pericardial friction rub was detected.

Pericardial effusion (Table I): PE was visualized by echocardiography in 16 patients. In 6 it was identified within 24 hours of the onset of chest pain. It was first detected on the third day in 6 others and the fifth day in 4. Serial echocardiograms indicated that no PE resolved completely before hospital discharge. The maximal size of the PE was estimated as small in 7 patients, moderate in 6 and large in 3.

Patients with PE had a higher peak creatine kinase level (1,769 ± 1,003) than those without (1,181 ± 838). More patients with PE were in Killip classification II, III or IV (11 of 16 [69%] vs 9 of 27 [33%]). There was a greater frequency of PE among women (10 of 16) than men (6 of 27). The age, weight, site of infarction, development of Q waves, history of AMI or use of heparin were not associated with the presence of PE.

There was not a close correlation between echocardiographically detected PE and pericardial chest pain. Of the 12 patients with pericardial pain, only 5 (42%) had PE and 11 patients with PE did not have pain. Likewise, there was not a significant association between the presence of a pericardial friction rub and PE (4 had both, 23 neither, 4 a rub without PE and 12 a PE without a rub). PE that was detected within the first 24 hours of an AMI could be unrelated to the acute event. In fact, only 1 of 6 patients with an early PE had typical chest pain with a rub. However, if these early PE are reclassified as no PE, there is still not a significant association between clinical pericarditis and PE.

Discussion

M-mode echocardiography is the procedure of choice for the detection of PE because it is accurate and noninvasive.[10,11] Effusions as small as 15 ml may be detected by M-mode echocardiography[7]; however, adipose tissue may cause a posterior echo-free space indistinguishable from PE.[12]

The incidence of early pericarditis after AMI has been variably reported as between 6 and 16% when diagnosed by the presence of a pericardial friction rub.[1–6] Pericardial chest pain suggestive of pericarditis was found in 28% of our patients, whereas 19% had pericardial friction rubs. A recent autopsy study of 85 patients who died within 6 months of an AMI found that 40% had pericarditis.[13]

Some investigators have stated that a detectable PE is rare after AMI.[1,4,14,15] Lichstein et al[1] reported that 6 patients with pericarditis soon after an AMI had echocardiograms that did not show significant PE. However, Kossowsky et al[15] reported 4 patients with pericardial chest pain who had angiographically documented PE within 2 weeks of an AMI; and in an autopsy series reported by Roeske et al,[13] 18% of patients had a PE. In a recent study by Wunderink,[16] M-mode echocardiography was done within 72 hours in 90 patients with

AMI and a PE was detected in only 5. The marked discrepancy in results is probably a reflection of differences in study design. In the present study 3 echocardiograms were performed on each patient by the same technician. In Wunderink's study each patient received a single echocardiogram that was done by 1 of 6 technicians.

A previous study by Markiewicz et al[17] showed no association between the presence of a pericardial friction rub and the amount of pericardial fluid detected by echocardiography. They describe 6 subjects with a typical clinical presentation of pericarditis, including a pericardial friction rub and no abnormal findings on M-mode echocardiography. Our results confirm that after AMI, chest pain suggestive of pericarditis is often not associated with an echocardiographically detected PE.

We conclude that PE as detected by M-mode echocardiography is frequently present after AMI, and its presence is not closely associated with the occurrence of a pericardial friction rub or typical pericardial pain.

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Contractile Properties of the Left Ventricle with Aneurysm

STEPHEN ARVAN, MD, and PEDRO BADILLO, MD

Twenty-five patients with an anterior wall acute myocardial infarction (AMI) were studied by 2-dimensional echocardiography (2-D echo) 3 to 5 days after the onset of chest pain, and serially over 3 to 24 months to determine if a particular pattern of contractility may predispose to left ventricular (LV) aneurysm formation. No subject had a prior AMI. In 8 subjects LV aneurysm eventually developed (group I), usually within 2 to 4 weeks of AMI; in 17 patients LV aneurysm did not develop (group II). Percent fractional shortening of the basal and midventricular segments was significantly better in group I subjects than in group II subjects (29 ± 2% vs 20 ± 2%, p <0.01, respectively, for the basal segment, and 23 ± 1% vs 17 ± 2%, p <0.02, respectively, for the midventricular segment). Infarct size as determined by peak creatine kinase isoenzyme levels was large in both groups, and there was no statistically significant difference between their mean values (2,099 ± 620 IU vs 1,334 ± 249 IU for groups I and II, respectively). Severe asynergy of the infarcted myocardium was present in all group I subjects and in 9 of 17 group II subjects on the initial 2-dimensional echocardiographic study. These results indicate that LV aneurysm formation depends on a critical imbalance of myocardial forces where strong LV segments cause bulging of weakened ones. (Am J Cardiol 1985;55:338–341)

Why left ventricular (LV) aneurysm develops in some patients after an anterior wall acute myocardial infarction (AMI) and not in others has never been adequately explained. Factors such as a large transmural AMI[1,2] and first AMI[3] have been associated with LV aneurysm formation, but neither condition provides a mechanistic concept for its development. Recent studies suggest that early changes in the shape of the ventricle as a result of "expansion" of freshly necrotic myocardium may be the geometric precondition necessary for its eventual development[4] Hemodynamic factors may play a major role in the pathogenesis of such post infarction topographic distortion. The LV contractile properties were therefore analyzed by 2-dimensional echocardiography (2-D echo) to examine specific changes that may help to explain the evolution of LV aneurysm.

Methods

Patients: Thirty-five consecutive patients admitted to the coronary care unit with the first episode of an anterior wall AMI were selected for this study. Two-dimensional echocardiograms were performed within 3 to 5 days after admission and then serially over several months after discharge. In 3 patients 2-D echo was technically difficult to perform, and these patients were excluded from the study; 7 patients were lost to follow-up. The total study population, therefore, consisted of 25 patients. Group I consisted of 8 LV aneurysm patients, 7 men and 1 woman, aged 64 ± 4 years (range 36 to 75), who were followed for 3 to 24 months (mean 10). Group II included 17 patients, 14 men and 3 women, aged 57 ± 3 years (range 32 to 76), in whom LV aneurysm did not develop after the first episode of an anterior wall AMI. The follow-up interval for group II was 3 to 12 months (mean 9). Three subjects in Group I (38%) and 7 in Group II (41%) had a history of hypertension.

Two-dimensional echocardiography: Two-dimensional echo was performed with a Varian 3000R phased-array ultrasonograph using a wide-angle (80°), 2.25-MHz transducer. A standard cross-sectional echocardiographic study was obtained in which the LV long-axis, multiple short-axis views, and apical views of the left ventricle were imaged. Abnormal wall motion was graded as akinetic, dyskinetic or severely hypokinetic only if more than 50% of the involved segment showed the abnormality.

Regional performance of the LV myocardium was analyzed in the apical 4-chamber view. After the transducer was angulated to image the greatest diameter of the left ventricle, the LV cavity was subdivided in a cephalocaudad direction into approximately equal thirds (Fig. 1). The reference plane for the basal segment was at an area just above the posterior aortic anulus and atrioventricular ring. For the midventricular plane, the reference point was at the region of the anterolateral papillary muscle and for the apical plane, the reference position was at a point equidistant between the anterolateral papillary muscle and the LV apex. Percent fractional shortening (%FS) of the minor axis of the base, midventricular and apical segments was determined by dividing the difference between

From the Division of Cardiology, University of Pittsburgh, and Montefiore Hospital, Pittsburgh, Pennsylvania. Manuscript received July 25, 1984; revised manuscript received October 8, 1984, accepted October 9, 1984.

Address for reprints: Stephen Arvan, MD, Montefiore Hospital, 3459 Fifth Avenue, Pittsburgh, Pennsylvania 15213.

the end-diastolic length (EDL) at the onset of the electrocardiographic R wave, and the end-systolic length (ESL), taken at the time of least separation of the septum and LV lateral wall, by the end-diastolic value (FS = EDL − ESL/EDL × 100). Distances were measured with an off-line computerized light pen, and %FS measurements were recorded after averaging the results of 3 separate cardiac cycles.

The diagnosis of an LV aneurysm was made on the apical 4-chamber view or the apical 2-chamber view of the left ventricle if there was persistent bulging of a thinned area of the LV myocardium in systole and diastole.[5,6]

Cardiac isoenzymes: Total creatine kinase levels as well as MB fractions were measured on admission and in 3 additional sequential plasma samples taken 8, 16 and 24 hours after the onset of chest pain, and then once every 24 hours until the levels returned to normal. The creatine kinase-MB isoenzyme was separated by the ion exchange column chromatography technique described by Mercer.[7] The normal range is 15 to 150 IU. A creatine kinase-MB level of greater than 2% when total creatine kinase activity is over 150 IU or a creatine kinase-MB value of greater than 3 IU when the creatine kinase is less than 150 IU was considered positive for AMI.

Interobserver variability: Reproducibility of %FS calculations of the basal, mid and apical segments was assessed by determining the percent difference from the average of duplicate measurements from 2 observers. The mean percent difference was calculated by averaging the absolute percent difference for the 25 subjects studied. Linear regression analysis was used to indicate the variability of the data about the identity line.

Statistics: Values for the echocardiographic variables were expressed as the mean ± standard error of the mean. Comparison of values in the various clinical groups were made with the unpaired Student *t* test. Changes were considered significant at p values <0.05.

Results

Percent FS values of the basal, mid and apical regions soon after an AMI and on follow-up examination are illustrated in Tables I and II. Basal and midventricular %FS were significantly better in group I than in group II patients ($p < 0.01$, and < 0.02, respectively) early after an AMI. Apical %FS was reduced equally in both groups. In the late follow-up period, basal segmental contractility remained significantly better in group I patients ($p < 0.01$), whereas the midventricular segments appeared equal and the apical region became significantly worse in group I than group II patients ($p < 0.001$).

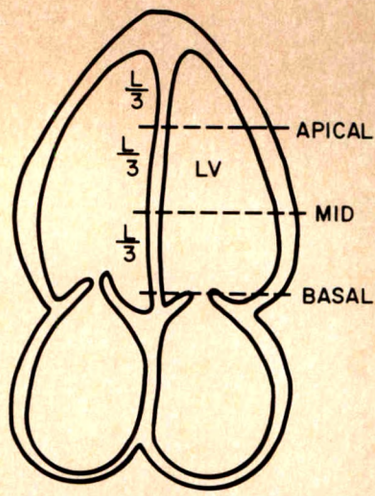

FIGURE 1. Regional contractility was measured by calculating percent fractional shortening at the base, midventricle and apex by dividing the major axis of the left ventricle (LV) into thirds starting at the base. L = long axis.

Nine subjects in group II had 1 or more segments that were dyskinetic in the apical 4- or 2-chamber view. Percent FS of the basal and midventricular segments was still better in group I than in group II patients with dyskinetic wall motion abnormalities (29 ± 2% vs 21 ± 2%, respectively, for the basal segment [$p < 0.02$] and 23 ± 1% vs 15 ± 2%, respectively, for the midventricular segment [$p < 0.01$]). Apical %FS values were not significantly different in the 2 groups (7 ± 2% vs 8 ± 2%, respectively).

Two-dimensional echocardiograms from a patient in group I in whom aneurysm developed are shown in Figure 2. One patient had a recurrent anterior wall AMI before a second study. In group II, a second anterior wall AMI developed in 3 patients and an inferior wall AMI

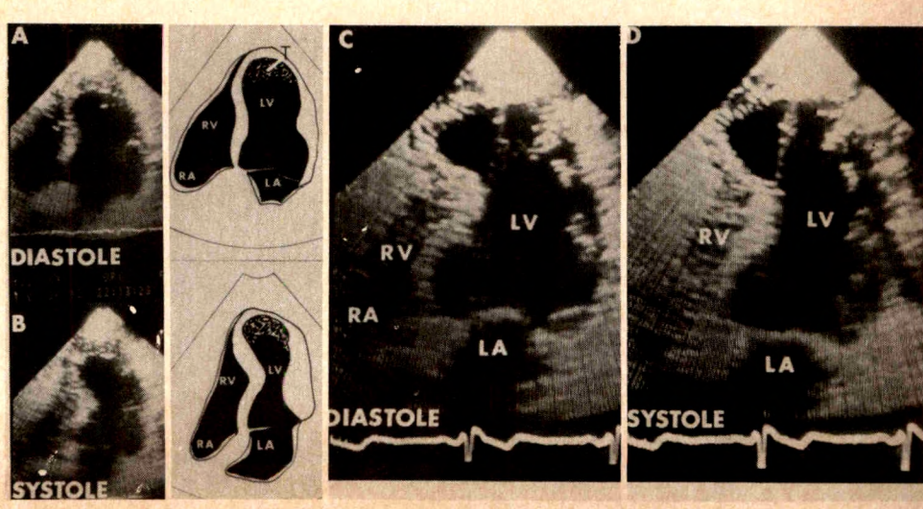

FIGURE 2. A and **B**, 2-dimensional echocardiogram shows slight infarct expansion at the apex and well preserved contractility of the basal and midventricular segments. **C** and **D**, 8 weeks after acute myocardial infarction, septal apical aneurysm developed. Contractility of the left ventricular base and midventricle is still well preserved. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; T = thrombus.

TABLE I Percent Fractional Shortening of Ventricular Segments in Patients with Left Ventricular Aneurysms

		%FS of LV Base		%FS of Mid LV		%FS of LV Apex	
Pt	Age (yr) & Sex	Early	Late	Early	Late	Early	Late
FG	71M	31	31	26	29	12	7
CK	69M	29	24	26	29	6	0
RR	36M	26	29	20	8	14	1
MK	58M	24	19	22	24	8	6
RB	61M	28	28	20	22	0	0
PZ	75F	38	36	20	18	4	2
SB	69M	25	27	22	20	0	2
IT	71M	33	39	26	26	10	3
Mean ± SEM	64 ± 4	29 ± 2	29 ± 2	23 ± 1	22 ± 2	7 ± 2	3 ± 1

%FS = percent fractional shortening; LV = left ventricle; SEM = standard error of the mean.

developed in 1 patient, with dramatic changes in his %FS (patient RJ).

The peak creatine kinase levels for group I subjects was 2,099 ± 620 IU; that for group II was 1,334 ± 249 IU. There was no statistically significant difference between the 2 groups, although 2 subjects in group II had a moderate to small AMI as judged by peak creatine kinase levels less than 350 IU.

Interobserver variability: Interobserver reproducibility was determined for FS values of the basal, mid and apical segments. The mean percent difference for the basal segment was 10%, for the midsegment 10% and for the apex 13%. The correlation coefficients were 0.94, 0.91, and 0.96, respectively.

Discussion

In 8 of 25 patients in the current investigation, LV aneurysm developed after anterior AMI. Percent FS values of the minor LV axis at the base, midventricle and apex showed that contractility was better in the basal and midventricular regions in these patients than in those in whom LV aneurysm did not develop. These changes were present on the initial 2-D echocardiograms performed 3 to 5 days after admission of an AMI, and on serial echocardiograms performed over 3 to 2 months. On the initial 2-D echocardiogram, 5 patients had no evidence of geometric distortion, but 3 had evidence of infarct expansion without a distinct aneurysm. On follow-up examination 7 of 8 patients had an LV aneurysm between the second and fourth week after AMI, and in 1 patient the aneurysm became apparent only at the eighth week after AMI. In group II, %FS remained similar or improved between studies among patients who did not have an intervening AMI. Midventricular and apical segments showed the most improvement.

The mechanism whereby augmented segmental LV performance leads to LV aneurysm formation is likely related to the influence of changes in wall stress. Strong contraction of the basal and, at times, the midventricular segments may generate enough LV systolic pressure to produce stretching and loss of geometric integrity of the weakened anteroapical segments. A similar mechanism had been proposed for dyskinetic wall motion abnormalities after ischemia or infarction.[9] In the absence of forceful contraction of the surrounding

TABLE II Percent Fractional Shortening of Ventricular Segments in Patients Without Left Ventricular Aneurysms

		%FS of LV Base		%FS of Mid LV		%FS of LV Apex	
Pt	Age (yr) & Sex	Early	Late	Early	Late	Early	Late
LF	73M	28	25	25	20	12	5
GS	59M	9	8	10	18	7	22
RM	41M	11	21	17	20	9	5
WC	65M	27	29	33	31	19	17
RD	49M	8	16	6	17	5	17
AB	63M	18	17	13	25	6	12
AR	44M	16	19	14	24	12	6
RJ*	72M	25	8	14	7	7	7
CB	54M	19	20	25	28	30	28
MB	62F	28	28	26	20	18	20
RB	32M	25	31	16	19	13	6
RV	50M	24	31	21	26	8	16
HP	55F	16	21	4	11	3	2
WR*	41M	25	19	25	16	15	8
SZ*	51M	24	22	25	11	12	11
LS	76M	18	21	12	15	2	8
JB*	74F	21	24	7	7	11	3
Mean ± SEM	57 ± 3	20 ± 2	21 ± 2	17 ± 2	19 ± 2	11 ± 2	11 ± 2

* Patients with recurrent infarction during follow-up study.
Abbreviations as in Table I.

myocardium, infarcted regions may maintain a normal LV contour because hemodynamic forces are insufficient to produce a critical increase in systolic pressure. This may explain the observation that an aneurysm tends to develop after a first AMI[3] when the uninvolved myocardium can still compensate for the loss of contractility of the infarcted myocardium.

Extensive myocardial necrosis has been cited as an important precursor in the development of an LV aneurysm.[3,8,10,11] In the present study, infarct size, as determined by peak creatine kinase levels, was large in patients in groups I and II. Mean values exceeded 1,300 IU in both instances. Statistically, there was no significant difference in peak creatine kinase values between the study groups. These results suggest that although LV aneurysm occurs after a large AMI, it is not the infarct size alone that determines its formation; other conditions must be present.

Initial wall motion abnormalities as detected by 2-D echo were more severe in group I than in group II subjects. This was particularly true for the LV apex, an area that was invariably involved either completely or partly by the LV aneurysm. In the former group, all patients showed dyskinesia or extensive akinesia of the apex, while in the latter group 8 of 17 patients demonstrated either hypokinesia or normal motion of the apex. Severe asynergy on 2-D echo correlates well with the presence of a transmural infarct.[5,12] A distinguishing feature on 2-D echo, therefore, was evidence of a transmural AMI involving the apex in group I and a lower incidence of the same pattern in group II. Nine of 17 patients in group II, however, had severe asynergy at the apex, yet they did not progress to aneurysm formation. On comparing %FS values of this subgroup with that for group I, there was still significantly greater %FS at the base in group I than in group II. Therefore, the presence of a transmural AMI alone does not explain LV aneurysm formation, but is one of the multifactoral conditions necessary for its development.

Limitations of the study: Interobserver variation in measuring segmental %FS was greatest for the apex (13%). The correlation coefficient was good ($r = 0.96$), however, indicating that there was concordance in interpreting the trend of contractility for the apical segment. Although reproducibility of apical %FS measurements appear low, the results may be misleading. Frequently the absolute FS values were small numbers and a difference of 1 or 2% between observers introduced a significant degree of variability.

The incidence of LV aneurysm after AMI could not be stated in this study because several patients were lost to follow-up or could not be included because of technical difficulty in performing 2-D echo. Although overall incidence of an LV aneurysm has been reported to vary between 4 to 20% after an AMI[13–15] by morphologic studies, the noninvasive estimate may differ since only the sickest patients are reported at autopsy.

Finally, %FS is a semiquantitative estimate of the state of contractility[16] and the results are influenced by angulation of the transducer and rotation of the heart. Perhaps an alternative method would be the assesment of wall thickening, which is uninfluenced by these factors.[17,18] Unfortunately, the epicardium is poorly defined around the full circumference of the left ventricle, particularly the lateral ventricular wall and the apical septal region. For this reason, we confined our measurements to the endocardial surface by calculating %FS along the minor axis of 3 identifiable segments.

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Assessment of Hemodynamic Significance of Isolated Stenoses of the Left Anterior Descending Coronary Artery Using Thallium-201 Myocardial Scintigraphy

VICTOR KALFF, MB BS, MICHAEL J. KELLY, MB BS, ALAN SOWARD, MB BS, RICHARD W. HARPER, MB BS, PHILIP J. CURRIE, MB BS, YEAN L. LIM, MB BS, PhD, and AUBREY PITT, MD

This study tests the hypothesis that the results of stress thallium-201 myocardial perfusion scans (Tl-201) are related to the mean transstenotic pressure gradient of coronary stenoses independent of the percent luminal diameter narrowing seen at angiography. The 22 study patients (20 men, 2 women, mean age 47 years, range 30 to 62) had no previous myocardial infarction. Each underwent a symptom-limited, erect bicycle Tl-201 test off antianginal therapy, shortly before percutaneous transluminal coronary angioplasty for isolated left anterior descending coronary artery stenosis. The percent narrowing, mean gradient at percutaneous transluminal coronary angioplasty and presence of a visually apparent Tl-201 defect were independently evaluated and results compared. All 4 patients with 90% or greater diameter narrowing had positive Tl-201 responses, and the mean gradient was 72 ± 11 mm Hg. Among the 18 patients with less than 90% diameter narrowing, the mean gradient was higher ($p < 0.001$) in the 11 with a positive Tl-201 (63 ± 15 mm Hg) than in the 7 with a negative Tl-201 (33 ± 20 mm Hg), but their percen narrowing did not differ significantly (72 ± 14% vs 66 ± 19%). Multiple regression analysis showe that the presence of a Tl-201 defect was a strong ($p = 0.003$) and percent narrowing ($p = 0.048$) a weak independent predictor for gradient. When the mean gradient was normalized for the prestenotic pressure, both percent narrowing ($p = 0.003$) and Tl-20 defects ($p = 0.006$) were significant independen predictors. Other variables, including age, locatio and length of stenosis, exercise electrocardio graphic ST-segment changes, hemodynamics workload and chest pain, did not enter the equation as significant independent predictors of gradient Therefore, Tl-201 adds valid information on th hemodynamic significance of a stenosis indepen dent of percent luminal diameter narrowing; this ma be of most value when percent narrowing is les than 90% and the clinical significance of a coronar stenosis is uncertain.

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In patients with myocardial ischemia, the degree of stenosis that is found at coronary angiography has traditionally been considered the most important variable against which all other tests attempting to assess coronary artery disease (CAD) have been compared.[1] However, angiography has limitations. Patients with angiographically similar degrees of stenosis have a wide range of coronary blood flow disturbance[2] and symptoms. Although routine measurement of absolute cor onary blood flow is not possible in patients, stress-in duced relative coronary blood flow changes can b examined using thallium-201 myocardial perfusio (Tl-201) scintigraphy.[3] However, in previous studie the scan findings were usually interpreted on the basi of the findings at coronary angiography without al lowing for the possibility that when these 2 tests yiel discrepant results, it may be because scintigraph produces a more valid reflection of the hemodynami significance of CAD than angiography.

Because it gives a physiologic measurement of th hemodynamic severity of a coronary stenosis, mea surement of the transstenotic pressure gradient durin percutaneous transluminal coronary angioplast

From the Department of Nuclear Medicine and Cardiology Service, Alfred Hospital, Melbourne, Victoria, Australia. This study was supported by the Alfred Hospital Whole Time Medical Specialists' Trust Fund. Manuscript received July 30, 1984; revised manuscript received October 15, 1984, accepted October 16, 1984.

Address for reprints: Victor Kalff, MB BS, Department of Nuclear Medicine, Alfred Hospital, Melbourne, Victoria 3181, Australia.

(PTCA)[4] provides a new chance to test the hypothesis that the results of Tl-201 scanning may add to standard coronary angiography in determining the true hemodynamic significance of individual stenoses. This question is particularly relevant when angiographic narrowing appears only moderate and the stenosis is of uncertain clinical significance. We have tested this hypothesis by comparing the results of coronary angiography, mean transstenotic gradients and exercise Tl-201 scanning in patients with isolated left anterior descending coronary artery (LAD) CAD undergoing PTCA.

Methods

Patients: All study patients underwent diagnostic coronary angiography for chest pain, and then stress Tl-201 scintigraphy followed by PTCA. The scan results did not influence the decision to proceed to PTCA. The study population comprised consecutive patients with (1) 1-vessel CAD of the LAD, (2) no electrocardiographic evidence, cardiac enzyme increase or history of myocardial infarction, (3) the ability to undergo erect bicycle exercise to more than 200 kpm/min or angina, and (4) successful pressure measurements at PTCA. Two women and 20 men fulfilled all these criteria. The mean age of these patients was 47 years (range 30 to 62).

Exercise thallium-201 scintigraphy: Beta-blocker and calcium antagonist therapy was withheld for more than 48 hours and nitrates more than 12 hours before a symptom-limited Tl-201 stress test using a continuous 3-minute/stage graded erect bicycle exercise protocol. Continuous electrocardiographic monitoring was performed throughout, with heart rate and 12-lead electrocardiogram recorded each minute, and blood pressure at 3-minute intervals. Two minutes before ceasing exercise, 1.5 to 2.0 mCi of Tl-201 was injected intravenously. Immediately after exercise, the patient was placed supine. After 3 minutes the precordial leads were removed and Tl-201 data were acquired on a Searle LEM gamma camera using a dual-energy window and high-resolution, low-energy collimator. Images were acquired in the 45° and 60° left anterior oblique, anterior and left lateral decubitus projections on photographic transparencies and as a 128 × 128 matrix image on a dedicated minicomputer (Digital Equipment Corp. PDP 11/34). Imaging duration for the postexercise and 2- to 3-hour delayed images was the time required to collect 300,000 counts for the first view.

Before PTCA, the Tl-201 transparencies and 20% thresholded computer images were qualitatively interpreted, using Dunn's criteria of normal or abnormal,[5] by 2 independent, experienced readers who had no knowledge of each patient's CAD status. If the scans were abnormal, the location of the defect was allotted to a coronary artery territory[6] and its severity graded qualitatively on a 4-point scale.

Angiographic and hemodynamic assessment at PTCA: PTCA was performed using the transfemoral approach.[4] In all patients this was performed within 48 hours of the Tl-201 stress test, except in 1 patient whose condition was clinically stable; this patient had PTCA 2 weeks later. Patients received premedication with sublingual nifedipine and received a continuous intravenous infusion of glyceryl trinitrate (50 to 100 μg/min) during PTCA. Multiple view coronary angiography of the LAD was performed using the Judkins technique. A 3.5 Fr Grüntzig balloon dilatation catheter was then passed across the lesion and mean arterial pressures recorded proximal and distal to the stenosis. Multiple balloon inflations were performed until no further reduction in lesion gradient could be achieved. Repeat pressures and gradients were then recorded, and a repeat multiview angiogram was taken.

To allow for variation in the mean transstenotic gradient resulting from changes in mean aortic pressures,[7] the mean gradient was divided by mean prestenotic pressure and this ratio defined as the normalized gradient. The stenosis before and after PTCA was measured from high-contrast, magnified cineagiographic images. The LAD was traced out, the diameter proximal and distal to the stenosis, and at the stenosis itself, measured in 2 views with Vernier calipers and the mean percentage luminal diameter narrowing (henceforth referred to as percent narrowing) was determined. The stenosis was considered to be proximal if it was between the origin of the LAD and its first septal perforator or first diagonal branch; middle if it was between these branches and the second diagonal branch; and distal if it was beyond the latter branch. Lesion length was estimated on a 4-point scale. The presence or absence of collaterals was also assessed visually.

Statistical analysis: Quantitative results are expressed as mean ± 1 standard deviation (range). Stepwise linear regression analysis was performed for assessment of predictors of transstenotic gradient. Univariate predictors of gradient were assessed with either Pearson's correlation coefficient, *t* tests or analysis of variance where appropriate. The standard error of the estimate (SEE) was defined as 1 standard deviation of the predictive error.

Results

At coronary angiography, 11 patients had a proximal and 11 a mid-LAD stenosis. Only 1 patient had collateral vessels. Maximal exercise-induced heart rate was 155 ± 24 beats/min (range 105 to 190); systolic blood pressure 193 ± 25 mm Hg (range 150 to 230), work load 802 ± 310 kpm/min (range 200 to 1,500); and exercise time 13 ± 4 minutes (range 2 to 20). Fifteen patients had a positive Tl-201 response, including the 8 with a positive electrocardiographic stress test (1 mm or more of ST-segment depression). Of the 11 with chest pain during exercise, 2 (workloads greater than 1,000 kpm/min, peak heart rates greater than 145 beats/min) had a normal Tl-201 response. All patients with an abnormal Tl-201 scan had defects corresponding only to the LAD territory.[6] There was no interobserver disagreement over the normality or abnormality of a Tl-201 study.

The mean arterial pressure at the time of transstenotic pressure gradient measurement was 90 ± 13 mm Hg (range 80 to 120). At univariate analysis, a weak but significant correlation ($r = 0.52$, $p < 0.05$, SEE = 19) was found between percent narrowing and mean transstenotic pressure gradient measured before PTCA; a slightly better correlation ($r = 0.64$, $p < 0.005$) was observed between percent narrowing and normalized gradient (Fig. 1). After PTCA, the mean gradient decreased from 55 ± 22 mm Hg (range 0 to 80) to 21 ± 21 mm Hg (range 0 to 39), and percent narrowing from 75 ± 17% (range 33 to 99%) to 27 ± 21% (range 0 to 58%). Combining the pre- and post-PTCA data widened the range of pressure gradients and percent narrowing, thus making the relation between gradient and percent narrowing ($r = 0.82$, $p < 0.0001$, SEE = 16) much more apparent.

Analysis of variance found no association between gradient and qualitative Tl-201 abnormality score in patients with a Tl-201 perfusion defect. Therefore, in all figures, Tl-201 scan results are shown as either pos-

TABLE I Multiple Regression Analysis

	Dependent Variables			
	Absolute Gradient		Normalized Gradient	
	F Value	p Value	F Value	p Value
Independently predictive variables				
Thallium score	12.0	0.003	9.5	0.006
% narrowing	4.5	0.048	11.9	0.003
Variables not predictive				
Exercise induced angina	3.4	0.08	0.9	0.4
Patient age	2.4	0.14	0.6	0.4
Maximal heart rate	2.3	0.15	1.4	0.2
Maximal blood pressure	0.4	0.5	0.4	0.6
Stenosis location	0.4	0.5	0.2	0.6
Maximal workload	0.2	0.7	0.0	1.0
Stenosis length	0.2	0.7	0.3	0.6
Exercise ST-segment changes	0.1	0.9	0.2	0.7
Duration of exercise	0.1	0.9	1.2	0.3

itive (abnormal perfusion defect) or negative (no perfusion defect). Figure 2 depicts the relation between Tl-201 scanning and absolute (Fig. 2A) or normalized transstenotic gradient (Fig. 2B). Those with a negative Tl-201 scan had a mean absolute gradient of 33 ± 20 (range 0 to 55) mm Hg and a normalized gradient of 0.40 ± 0.24 (0 to 0.60); those with positive scans had an absolute gradient of 65 ± 14 (40 to 80) mm Hg and a normalized gradient of 0.70 ± 11 (range 0.51 to 0.84).

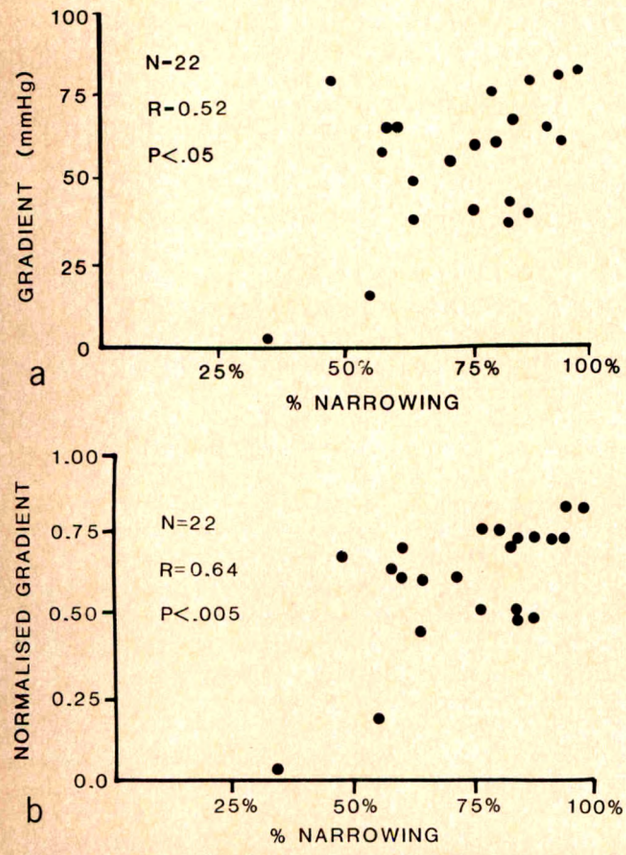

FIGURE 1. The relation between percent luminal diameter narrowing and (**a**) mean gradient and (**b**) normalized transstenotic pressure gradients. The correlation is slightly better for normalized than for absolute gradient, although in both cases there is a wide scatter of results. The normalized gradient is calculated as the mean transstenotic gradient/mean prestenotic pressure.

Results of multivariate analysis are summarized in Table I. With either mean transstenotic gradient or normalized gradient as the dependent variable, only Tl-201 results and percent narrowing were significant independent predictors, and percent narrowing was a better predictor of normalized than absolute gradient.

Figure 3 shows the relation between percent narrowing, transstenotic gradient and a positive or negative Tl-201 study. In the 18 patients with percent narrowing less than 90%, the mean gradient was significantly higher ($p < 0.001$) in those with a positive (63 ± 15 mm Hg) than those with a negative Tl-201 scan (33 ± 20 mm Hg), while their mean percent narrowing did not differ significantly (72 ± 14% vs 66 ± 19%).

Discussion

This study has shown that for a given degree of angiographically defined coronary artery stenosis, exercise Tl-201 myocardial perfusion scintigraphy can demonstrate a variable ability to augment coronary blood flow with stress, and that this variability is related to another hemodynamic measurement of lesion severity: the transstenotic pressure gradient.

Coronary angiography has the major role in assessing patients presenting with chest pain suggestive of myocardial ischemia. Nevertheless, it has important limitations. It may underestimate the significance of a stenosis if there is surrounding diffuse narrowing[8] or spasm during physical or emotional stress.[9] Overestimation is likely if spasm occurs during angiography. Significant interobserver variability in visual interpretation of lesions[10] has led to computer-assisted quantitation of absolute diameter narrowing.[11] However, a universally acceptable system is not available because of problems with variation in vessel caliber,[12] irregular, eccentric or serial lesions, contrast streaming through a lesion and effects of collateral vessels.[9,13] These difficulties have led to a search for supplementary methods of assessing the significance of CAD.

One such method, measurement of transstenotic pressure gradient, was used in this study as an indicator

of flow disturbances because it can be readily performed during PTCA.[4] This measurement has its own limitations in that it is necessarily invasive and overestimating true gradient by further occlusion of the stenosis by the catheter itself.[14] However, this overestimation, is relatively systematic,[14] and thus does not alter our overall findings. Because lesion gradient may change with varying aortic pressures,[7] a normalized gradient measurement was also used. This showed that Tl-201 scintigraphy still provides significant independent information about lesion hemodynamics.

Despite its deficiencies, transstenotic gradient correlates well with other physiologic measurements of coronary blood flow disturbance such as coronary flow reserve,[15] thought to characterize more truly the functional significance of a coronary lesion than percent stenosis.[2,16] White et al[2] directly measured coronary flow reserve in a group of patients undergoing coronary artery bypass surgery and found that it correlated poorly with angiographically determined percent stenosis. They questioned the use of angiographic measurements alone to determine the need for surgery. Our results agree with theirs in that the range of hemodynamic abnormality for a given percent stenosis was large despite a significant correlation between percent stenosis and gradient. More recently, Harrison et al[12] found that the absolute cross-sectional area of a stenosis, a variable that could not be measured in our study, correlated with coronary flow reserve better than did percent stenosis. Their data provide further evidence that the diffuse nature of CAD limits the usefulness of percent stenosis in determining the true significance of coronary narrowings.[8] However, absolute cross-sectional area measurement is itself of limited clinical value in that it requires sophisticated analysis that can only be meaningfully interpreted in vessels if their normal caliber is known, an uncommon situation. Furthermore, it cannot reflect the hemodynamic effects of the exercise-induced spasm that occurs in many patients.[9]

Tl-201 scanning was used in this study because it is minimally invasive and its myocardial uptake is linear over a wide range of coronary blood flow rates.[3] It is applicable to vessels of varying caliber,[12] and can reflect the effects of exercise induced spasm and collateralization.[9] Our finding that abnormal Tl-201 scans were associated with higher transstenotic pressure gradients

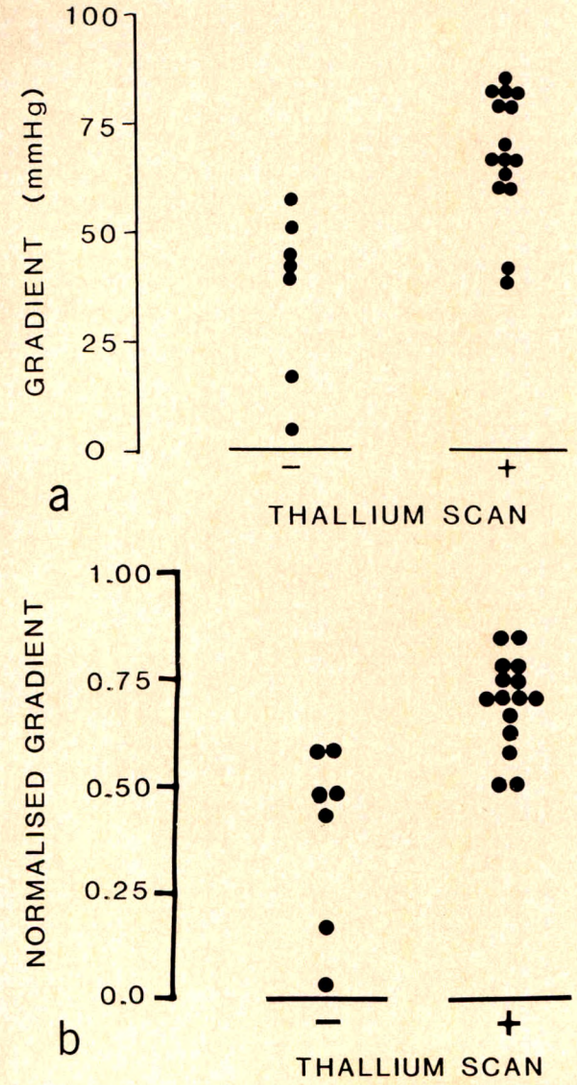

FIGURE 2. The relation between positive (+) or negative (−) thallium-201 scan results and (**a**) absolute gradient and (**b**) normalized transstenotic pressure gradient. The best separation of positive and negative thallium-201 scan results occurs at an absolute gradient of about 50 mm Hg (**a**) and a normalized gradient of about 0.5 (**b**).

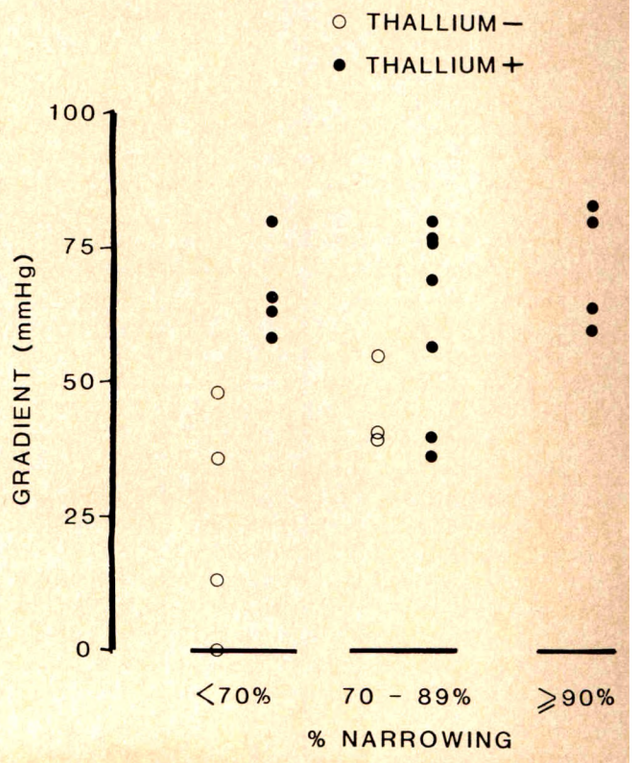

FIGURE 3. The relation between percent luminal diameter narrowing, mean transstenotic pressure gradient and the finding of a positive or negative thallium-201 study. A positive scan result was always associated with a high transstenotic gradient regardless of the percent luminal diameter narrowing.

is similar to that of Bateman et al.[17] However, their absolute pressure gradient threshold for the development of a Tl-201 defect was much lower than ours because their data were collected during open heart surgery, which is accompanied by arterial hypotension. The normalized gradient results between the 2 studies are more comparable, especially when the systematic overestimation of our gradient data that results from the PTCA catheter is considered. Our results showing the independent predictive value of Tl-201 scanning are supported by those of LeGrand et al,[18] who demonstrated that coronary flow reserve correlates better with Tl-201 results than with percent stenosis

Tl-201 scanning has its own deficiencies, with qualitative interpretation requiring experienced observers and a universally acceptable method of quantitative analysis yet to be agreed upon.[3,19] Nevertheless, this study shows that scintigraphy provides unique data relative to the effect of a stenosis on coronary blood flow, a factor that may be important in the evaluation of the individual patient with CAD.

Clinical implications: Evidence is accumulating that a negative Tl-201 stress test is associated with a good long-term prognosis regardless of the coronary anatomy[20] and that scintigraphic detection of myocardial ischemia at stress Tl-201 scintigraphy is a strong predictor of cardiac events in patients with known CAD.[21] The results of our study document a physiologic basis for these observations and lessen the clinical concern that Tl-201 scanning may miss CAD that appears to be significant on angiographic criteria.[22]

Extrapolation of the data obtained in this study to the general clinical applicability of Tl-201 scintigraphy must be done with caution. Our patient population was highly selected, and results different from ours may be expected in patients with previous myocardial infarction, receiving antianginal medication during the stress test, or whose coronary stenoses were multiple or involved vessels other than the LAD.

Our data are most directly applicable to those patients with 1-vessel LAD CAD whose symptoms are atypical and in whom the percent stenosis is not severe. In our study, a positive scan result always indicated a hemodynamically significant stenosis regardless of the angiographic findings. A negative Tl-201 scan was associated with a significantly lower gradient, but one that was still somewhat greater than that found after successful PTCA.[4] Thus, qualitative assessment of Tl-201 scintigrams permits identification of moderate and severe hemodynamic disturbances, but not the milder abnormalities—a potential limitation of this test. However, improvement in detection of these milder abnormalities may be possible with spatial and temporal quantitation of Tl-201 perfusion images,[17,19] tomographic Tl-201 imaging[23] or a more potent form of stress such as a supine bicycle[24] or treadmill[25] exercise test.

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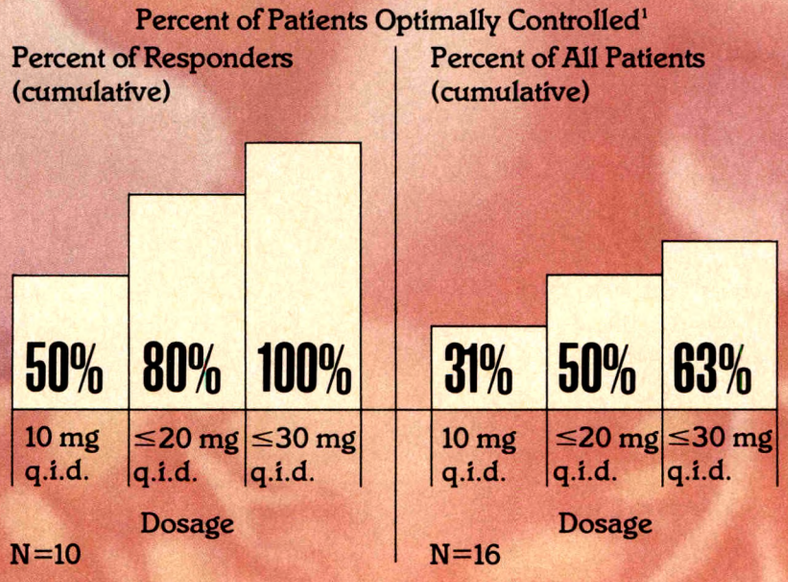

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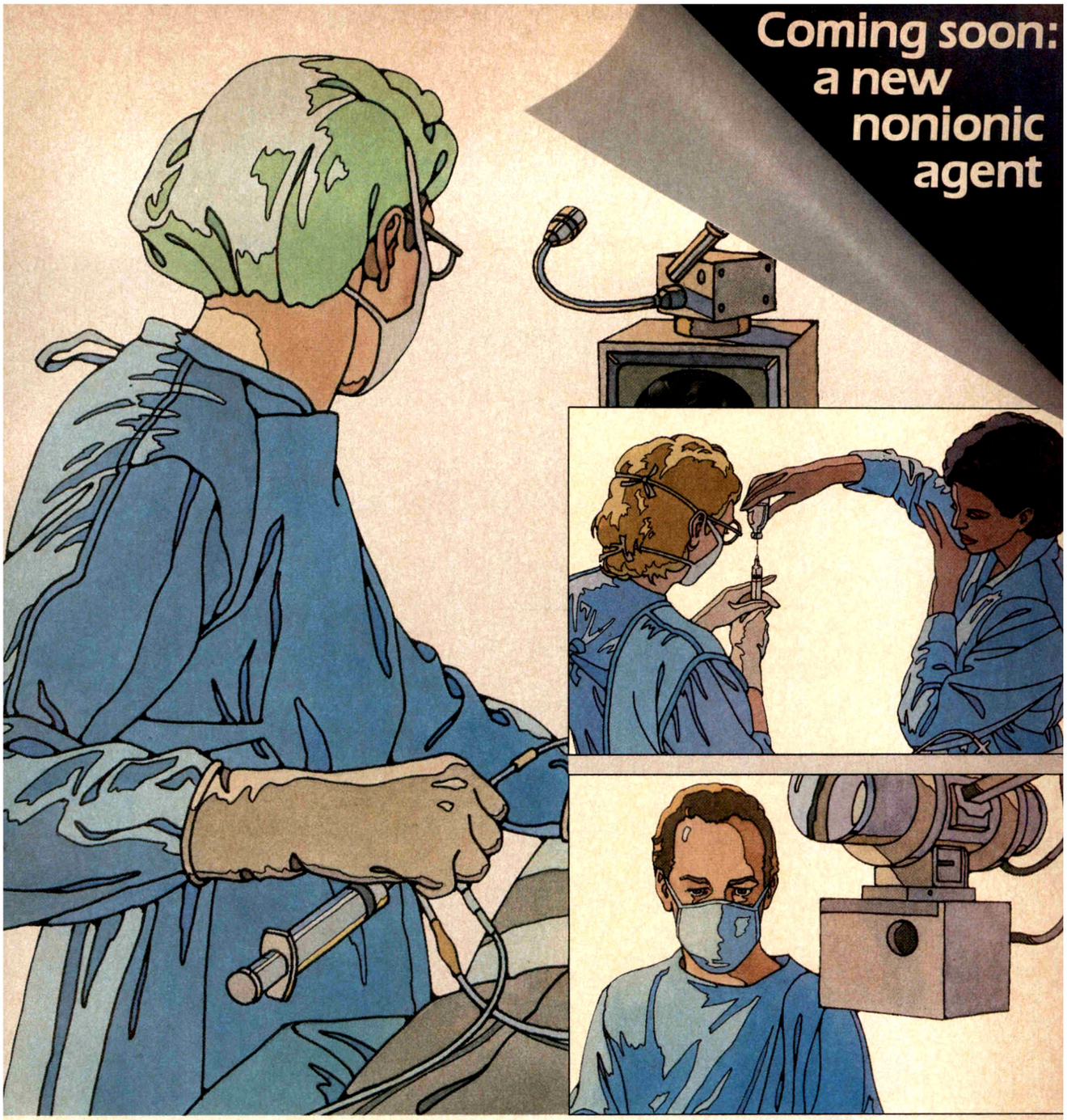

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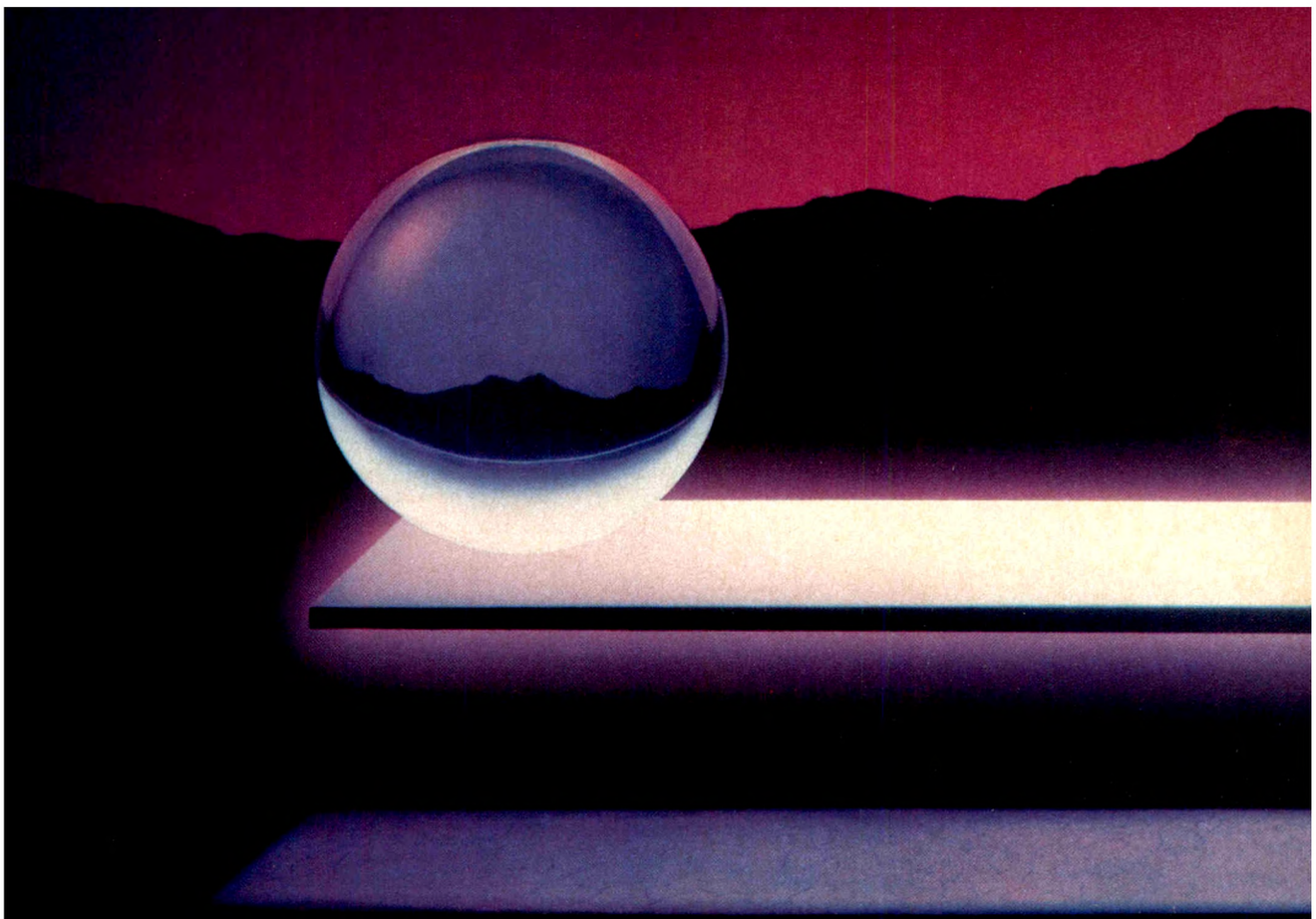

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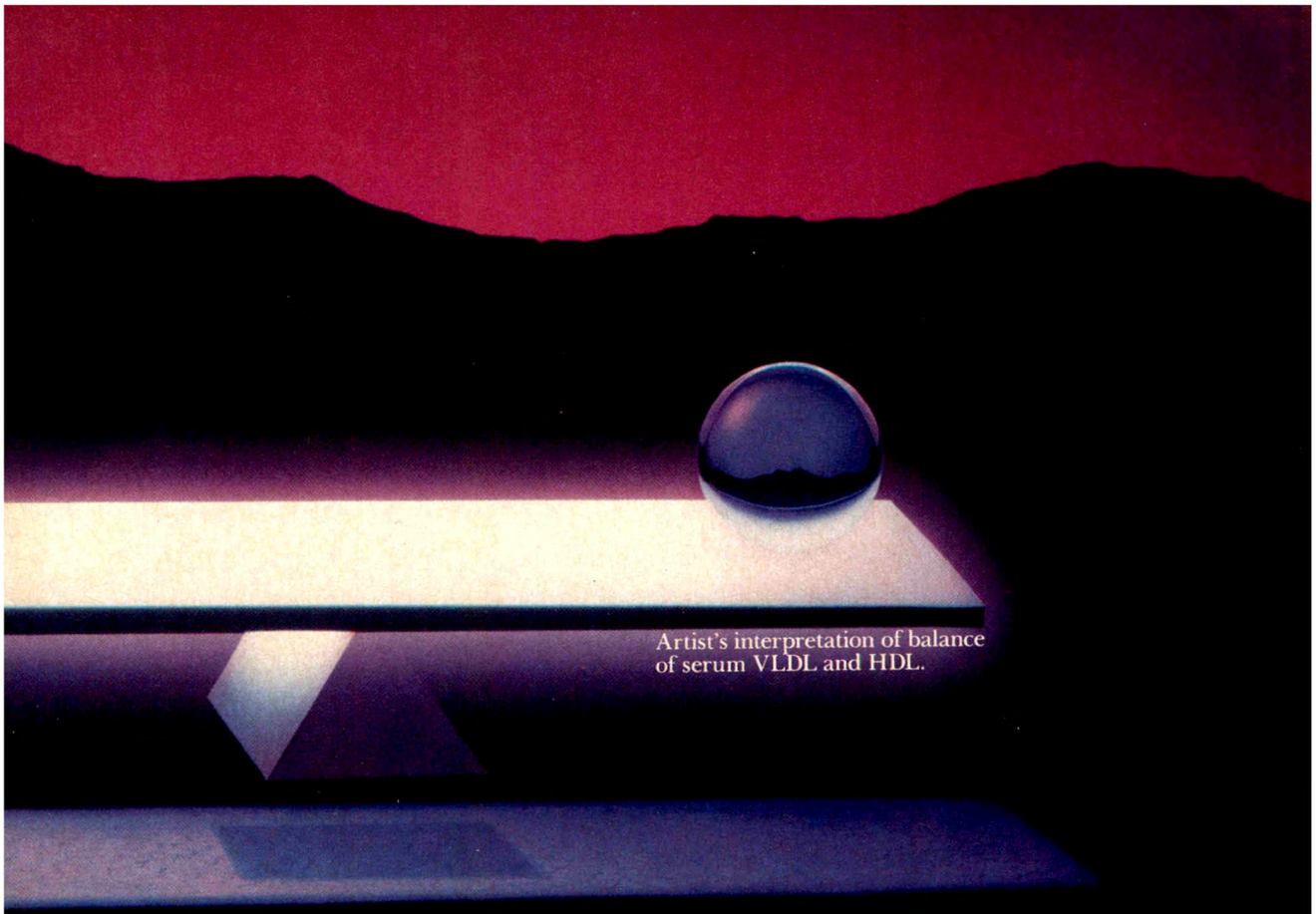

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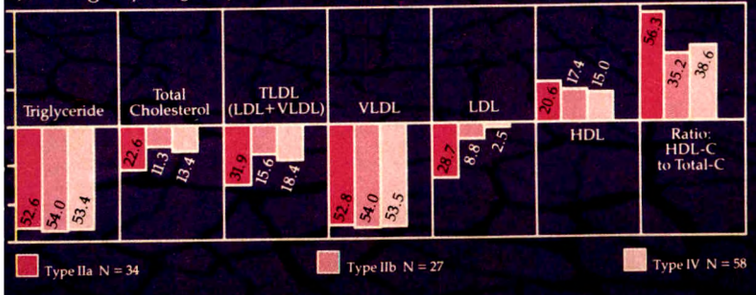

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CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO
		Total	VLDL	LDL	HDL	HDL Cholesterol / Total Cholesterol
IIa	−44%	−4.2%	−44.3%	− 5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	− 6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil capsules, USP) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (see WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings.)

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil capsules, USP) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria
Central Nervous System: headache, dizziness, blurred vision
Musculoskeletal: painful extremities
Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia
Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints
Central Nervous System: vertigo, insomnia, paresthesia, tinnitus
Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL CAPSULES, USP). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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Clinical, Angiographic, Hemodynamic, Perfusional and Functional Changes After One-Vessel Left Anterior Descending Coronary Angioplasty

ROBERT D. OKADA, MD, YEAN L. LIM, MD, CHARLES A. BOUCHER, MD, GERALD M. POHOST, MD, DAVID A. CHESLER, ScD, and PETER C. BLOCK, MD

Percutaneous transluminal coronary angioplasty (PTCA) was successfully performed in 20 patients with 1-vessel left anterior descending (LAD) coronary artery disease. Exercise capacity in terms of peak workload, heart rate and systolic blood pressure all increased significantly 1 week after PTCA. All patients had some decrease in stenosis size and gradient. All patients except 1 had an improvement in functional class. Eight of 12 patients with abnormal exercise electrocardiograms before PTCA had normal electrocardiograms after the procedure. Exercise thallium-201 (Tl-201) myocardial perfusion images obtained in all 20 patients before and 1 week after PTCA were analyzed using a new computer method designed to quantitate regional myocardial Tl-201 distribution, redistribution and clearance rate. Significant improvement in Tl-201 activity was present in the anterior and septal segments of the left ventricle 1 week after PTCA. This increase in Tl-201 uptake was associated with a significant reduction in the amount of Tl-201 redistribution between initial and delayed postexercise images in the same regions. Tl-201 clearance rate in the segments supplied by the dilated vessel also improved significantly. Abnormal Tl-201 lung uptake was seen in 17 patients before and in 4 patients after PTCA. Exercise ejection fraction response and septal wall motion also improved after PTCA of the LAD stenosis in all 17 patients who had exercise radionuclide ventriculography. Improvement in clinical, angiographic and hemodynamic factors as well as in global and regional myocardial perfusion and function occurs after PTCA for 1-vessel LAD coronary artery disease.

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Percutaneous transluminal coronary angioplasty (PTCA) has become an accepted alternative to coronary artery bypass graft surgery for treating selected patients with coronary artery disease (CAD).[1,2] Data on short- and long-term improvement in myocardial perfusion and function after successful PTCA are steadily emerging.[3–10] This study describes our experience in the short- and long-term follow-up studies of the clinical, angiographic, hemodynamic, perfusional and functional effects of PTCA in patients with 1-vessel left anterior descending (LAD) CAD. A new computer method was used to quantitate regional myocardial perfusion from serial exercise thallium-201 (Tl-201) scintigraphic scans using a technique that allows direct comparison of Tl-201 perfusion in the same anatomic region of the myocardium before and after PTCA.

From the Cardiac Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. This study was supported in part by Grants HL-21751 and HL-26215 from the U.S. Public Health Service, Bethesda, Maryland. Manuscript received June 1, 1984; revised manuscript received October 24, 1984, accepted October 25, 1984.

Address for reprints: Robert D. Okada, MD, Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114.

Methods

Patient group: The study population was derived from 37 patients admitted to the Massachusetts General Hospital for PTCA of 1-vessel CAD. The procedure was technically successful in 25 patients. Twenty of these patients had exercise Tl-201 scintigraphy before and after PTCA. These 20 patients constituted the study group, which included 16 men and 4 women, aged 35 to 63 years (mean 51 ± 7) (Fig. 1). Seventeen patients also had radionuclide ventriculography at rest and during exercise. Three patients had previously documented myocardial infarcts. Selective coronary arteriography revealed proximal narrowing in excess of 60% of the luminal diameter, confined to the LAD in 19 patients. One patient had 2 critical narrowings, 1 in the LAD and the other in the diagonal branch of the LAD. All patients had stable but progressive angina (13 were in New York Heart Association class II, 6 were in class III and 1 in class IV) for periods of 3 to 18 months (mean 7 ± 4). All patients were poorly controlled with medical therapy

and were considered suitable for coronary artery bypass graft surgery. None had undergone previous aortocoronary bypass graft surgery. During exercise testing before PTCA, propranolol and long-acting nitrates were not discontinued. Immediately after successful PTCA, β-blocking drugs were discontinued but long-acting nitrates and aspirin were continued for 6 months after PTCA. Exercise Tl-201 scintigraphy and radionuclide ventriculography were performed within 48 hours before and 1 week after PTCA. Nine patients underwent repeat study 6 months after PTCA. Successful PTCA was defined as a reduction in pressure gradient across the narrowing measured during pullback of the dilating catheter or reduction in luminal narrowing at the site of the lesion.

Thallium-201 myocardial scintigraphy: Symptom-limited exercise was performed on a bicycle ergometer in the upright position using a previously described protocol.[11] One minute before the anticipated cessation of exercise, 1.5 to 2.0 mCi of thallium-201 chloride (New England Nuclear) was administered intravenously. An initial postexercise image in the anterior view was collected within 5 minutes after stopping exercise. Intermediate and delayed redistribution images were collected approximately 30 and 180 minutes, respectively, after the initial injection of Tl-201. Ten-minute collections of scintigraphic data were acquired in the anterior, 50° and 70° left anterior oblique (LAO) projections using a conventional Anger scintillation camera (Picker Dynamo Mobile Gamma Camera) interfaced with a mobile nuclear medicine computer system (MUGA-CART, Medical Data Systems). An all-purpose, medium-resolution, parallel-hole collimator and a 25% energy window, encompassing x-ray emissions of 60 to 80 keV, were used. Data was transferred to a VAX 11/780 (Digital Equipment Corp.). The images were then displayed using a DeAnza system teledisplay unit.

The ST-T-wave response to exercise was considered abnormal if there was at least 1 mm horizontal or downsloping ST-segment depression 0.08 second after the J point.

Quantitative interpretation of thallium-201 images: A new computer-assisted method of analyzing Tl-201 images was developed and validated in our laboratory.[12,13] Briefly, an ellipse is placed around the left ventricular (LV) activity in 1 of the 3 serial Tl-201 images. Automatic realignment of the LV activities of the other 2 serial images to fit into the drawn ellipse is performed by horizontal and vertical translation as well as rotation of the images by computer cross-correlation. Background subtraction is performed for each pixel (p) within the original ellipse, taking into account the activity (i) in a "background ellipse," the distance (d) between the pixel point and the background ellipse, and the angle subtended by the 2 adjacent pixels to i from p (Fig. 2). Tl-201 activities in the 3 serial images are normalized to the hottest pixel in the initial postexercise image after a 9-point smoothing. The Tl-201 activity profile curve for the LV myocardium in each image is then determined by the maximal mean peak activity of a running average in 3 pixels within the myocardium on a line perpendicular to the tangent of approximately 200 equally spaced points on the elliptical perimeter. The remainder of the ellipse is subdivided into 5 equal segments along the perimeter and the segments are designated 1 to 5 in a clockwise manner (Fig. 3). To estimate regional myocardial perfusion, mean Tl-201 activity in segments 1 and

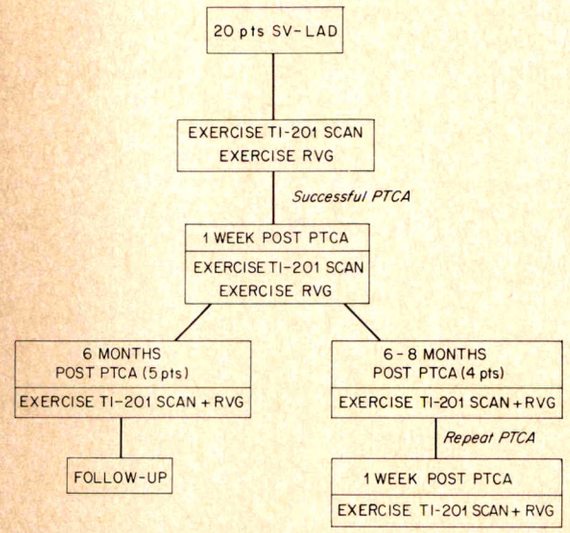

FIGURE 1. Breakdown of patient study group: PTCA = percutaneous transluminal coronary angioplasty; RVG = radionuclide ventriculogram; SV-LAD = single-vessel coronary artery disease involving the left anterior descending (LAD) branch; Tl = thallium.

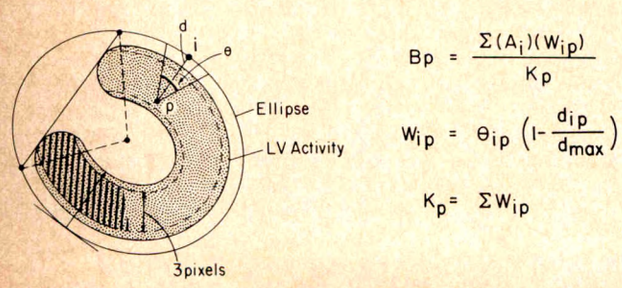

FIGURE 2. Fitting of ellipse (e) around left ventricular (LV) activity (i), background subtraction algorithms, elimination of basal nonmyocardial portion of ellipse and the determination of thallium-201 activity profile from highest mean activity of a 3-pixel (p) wide band within the LV myocardium (see text for details).

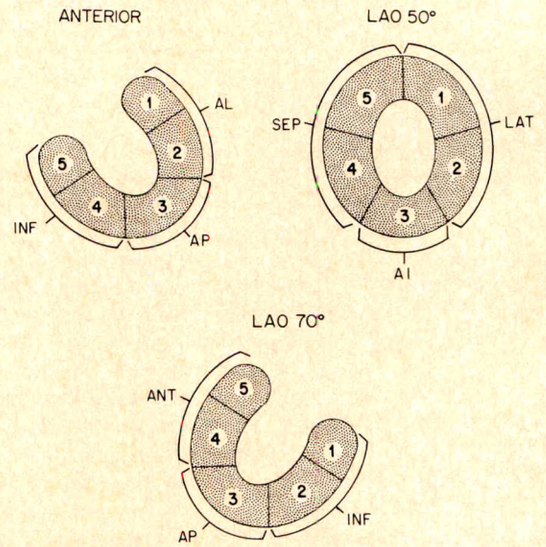

FIGURE 3. Quantitative and qualitative segmentation of left ventricle in relation to coronary artery perfusion territories: AI = apicoinferior; AL = anterolateral; ANT = anterior; AP = apical; INF = inferior; LAO = left anterior oblique; LAT = lateral; SEP = septal; the AL, ANT and SEP segments are in the left anterior descending coronary artery territories; the LAT segment is in the left circumflex coronary artery territory; the INF segments are in the right coronary artery territories.

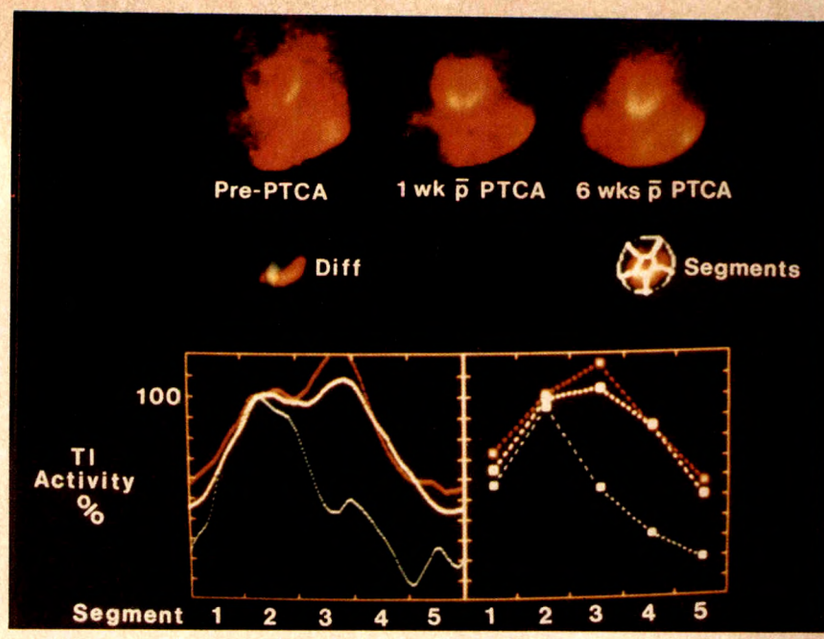

FIGURE 4. Quantitative thallium-201 (TI) activity curves showing segmental TI-201 distribution in the initial postexercise images before, 1 week and 6 months after percutaneous transluminal coronary angioplasty (PTCA) in the left anterior oblique 50° view in 1 patient.

2 in the anterior view (anterolateral segment), segments 4 and 5 in the LAO 45° view (septal segment) and segments 4 and 5 in the 70° LAO view (anterior segment) were ascribed to the LAD territory. Segments 1 and 2 in the 45° LAO view were ascribed to the left circumflex coronary artery distribution. Segments 4 and 5 in the anterior view and segments 1 and 2 in the 70° LAO view were ascribed to the posterior descending coronary artery. The apical segment in each of the 3 views was not ascribed to any 1 specific coronary artery because of overlap of coronary distribution in this region. Mean normalized regional Tl-201 activity of each of the 5 segments in each image was then calculated and plotted in graphic form (Fig. 4). The difference in normalized Tl-201 activity in each segment (delayed minus initial) was taken to represent the amount of regional redistribution of the tracer activity between the delayed and initial images. In addition, the computer-realigned, background-subtracted and normalized Tl-201 image acquired immediately after exercise was directly subtracted from the delayed image after exercise to produce an intensity-coded color functional difference image depicting areas of ischemia-induced Tl-201 redistribution (Fig. 5).

For PTCA scan comparison, the initial postexercise images obtained before and after PTCA were treated as serial images and analyzed using the new computer program. Count activities in the images acquired before, 1 week after and 6 months after PTCA were normalized to the hottest pixel in the initial postexercise image before PTCA (Fig. 4). Improvement in regional Tl-201 uptake was defined as an increase of 10%.

Regional myocardial thallium-201 clearance rate: Using the computer analysis, regional Tl-201 clearance in each LV segment was also quantitated. The clearance rate in each segment, expressed as a mean half-time ($t^{1}/_{2}$ in hours) was calculated by fitting a monoexponential function to the initial, intermediate and delayed image activities.

Qualitative interpretation of thallium-201 images: Images were interpreted qualitatively by 2 experienced observers. The left ventricle was subjectively separated into 3 segments in each projection (Fig. 3). Tl-201 activity in each segment was graded qualitatively on a scale of 0 to 2: 0 = absent activity; 1 = definitely reduced but not absent activity; and 2 = normal. Half grades were used to indicate activity that was either severely but not completely absent (grade 0.5) or activity that was only slightly reduced from normal (grade 1.5). Segments that had abnormally reduced activity (1.0 or less) on the initial view but showed an increase by at least 0.5 grade on the delayed view were considered to have transient defects. Improvement in regional Tl-201 uptake after PTCA was defined as an increase in the mean score of at least 0.5. The intensity of lung Tl-201 activity in the immediate postexercise image was also assessed qualitatively on a scale of 0 to 2: 0 =

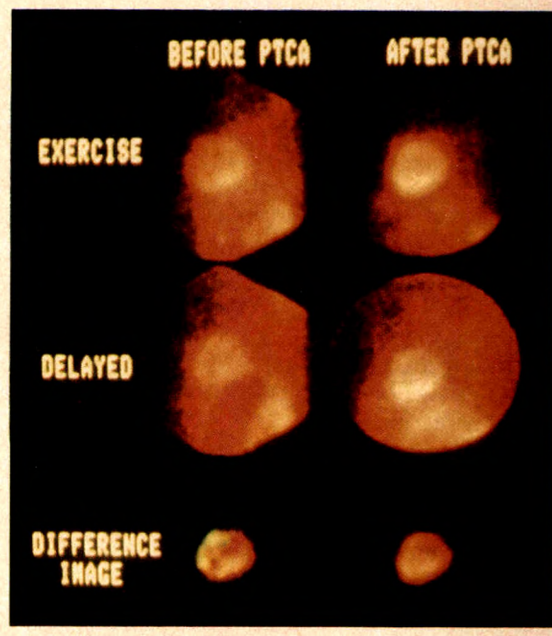

FIGURE 5. Changes in the difference image (delayed-initial) before and 1 week after percutaneous transluminal coronary angioplasty (PTCA). Green color depicts presence of thallium-201 redistribution between the initial and delayed postexercise images.

TABLE I Clinical and Angiographic Changes After Percutaneous Transluminal Coronary Angioplasty

	NYHA Class			% LAD Stenosis		Pressure Gradient (mm Hg)	
Pt	B	A1	A6	Before	After	Before	After
1	3	1	1	95	50	—	—
2	2	1	1	99	10	60	13
3	3	2	3	85	30	50	15
4	2	1	1	95	10	50	15
5	3	1	1	85	50	30	15
6	2	2	—	95	45	60	25
7	2	1	1	85	20	50	25
8	4	2	—	70	40	10	10
9	3	1	—	90	65	58	18
10	3	2	3	90	30	60	35
11	2	1	—	90	20	65	20
12	2	1	—	85	25	—	—
13	2	1	—	80	0	45	15
14	2	1	3	80	25	40	0
15	2	1	—	60	50	30	25
16	2	1	—	95	20	60	15
17	3	2	3	95	40	80	20
18	2	1	—	90	20	60	15
19	2	1	—	70	10	50	20
20	2	1	—	80	30	45	15
Mean	2.4 *	1.3	1.9	85.7 *	29.5	50.2 *	17.6
± SD	±0.6	±0.4	±1.1	±10.1	±16.9	±15.8	±7.4

* $p \leq 0.001$ between adjacent values.
A1 = 1 week after percutaneous transluminal coronary angioplasty (PTCA); A6 = 6 months after PTCA; B = before PTCA; LAD = left anterior descending artery; NYHA = New York Heart Association; SD = standard deviation; — = not done.

normal activity; 2 = lung and myocardial activity of the same intensity.[14] Lung Tl-201 activity scores of +1 or +2 were considered abnormal.

Exercise radionuclide ventriculography: Rest and exercise gated blood pool scans were acquired in 17 patients after acquisition of delayed Tl-201 images before and after PTCA. The technique used to acquire rest and exercise gated blood pool scans has been previously described.[11]

Analysis of radionuclide ventriculography: Rest and exercise LV ejection fractions were derived from the LAO views using a previously described semiautomated edge detection with a variable region of interest program.[15] Regional LV wall motion was evaluated subjectively as previously described.[12] Three segments in each projection were evaluated: anterolateral, apical and inferior segments in the anterior view; and septal, apicoinferior and posterior segments in the LAO view. Wall motion in each segment was graded on a 0.5 point increment scale from 3 (normal) to −1 (dyskinesia).

Evaluation of the severity of coronary artery stenosis: The severity of a coronary artery stenosis was expressed as a percentage of the pre- and poststenotic luminal diameter. The narrowest portion of the vessel lumen at the site of the stenosis and the normal luminal diameter proximal and distal to the stenosis were measured in at least 3 oblique views in the selected coronary angiograms obtained before and after PTCA. The mean of all individual measurements was calculated. Pressure gradients across the stenosis were measured before and after inflation of the balloon at the stenotic site in all but 2 patients; in the latter 2 the pressure gradients could not be measured because of occlusion of the guiding catheter.

Statistical analysis: Clinical, exercise, radionuclide ventriculographic and Tl-201 data before and 1 week after PTCA in all 20 patients were compared. In 9 patients, data obtained at approximately 6 months after PTCA were also analyzed. For the quantitative analysis of Tl-201 images, regional Tl-201 uptake in the initial postexercise images before and after PTCA were compared. Then, differences in normalized regional Tl-201 uptake between early and delayed images, taken to represent redistribution, before and after PTCA were also compared. Finally, mean clearance of Tl-201 in counts/pixel and clearance rate ($t_{1/2}$) in each LV segment before and 1 week after PTCA were compared.

All data are expressed as mean ± standard deviation. The Student *t* test for paired data was used to evaluate differences between data obtained in the 20 patients both before and 1 week after PTCA. Differences in values between 1 week and 6 months after PTCA were assessed by the analysis of variance with the difference between data before and 1 week after PTCA as covariate. The difference in changes in regional Tl-201 distribution at 1 week after PTCA between patients that required repeat PTCA and those that did not was analyzed using the analysis of variance.

Results

Clinical, angiographic and hemodynamic changes (Table I): In terms of an alleviation of angina, all patients except 1 (no. 6) had improvement in functional class at 1 week after PTCA. The mean functional class improved significantly at 1 week (Fig. 6). In 4 patients (nos. 3, 10, 14 and 17), however, chest pain severe enough to warrant repeat coronary angiography and a second PTCA recurred within 2 to 8 months after the initial procedure. All 20 patients included in the present study had varying degrees of success in the dilatation of their LAD stenosis. The mean percent luminal LAD stenosis decreased significantly after PTCA (Fig. 7). The mean pressure gradient across the stenotic lesion decreased significantly immediately after successful

TABLE II Exercise Variables Before and After Angioplasty

Variables	Before PTCA (n = 20)	1 Week After PTCA (n = 20)	6 Months After PTCA (n = 9)
Peak workload (kpm)	79 ± 33	104 ± 37*	104 ± 56
Ex time (min)	9 ± 4	12 ± 4†	14 ± 5
Rest HR (beats/min)	61 ± 10	68 ± 11‡	70 ± 10
Ex HR (beats/min)	113 ± 21	136 ± 22§	137 ± 34
Rest SBP (mm Hg)	128 ± 18	132 ± 17	130 ± 16
Ex SBP (mm Hg)	154 ± 21	176 ± 26†	186 ± 22‡
Rest EF (%)	61 ± 7	62 ± 8	72 ± 14
Ex EF (%)	58 ± 9	66 ± 11*	71 ± 14

* $p < 0.01$ compared with previous value; † $p < 0.0001$ compared with previous value; ‡ $p < 0.05$ compared with previous value; § $p < 0.001$ compared with previous value.
EF = ejection fraction; Ex = exercise; HR = heart rate; PTCA = percutaneous transluminal coronary angioplasty; SBP = systolic blood pressure.

dilatation (Fig. 7). None of the 20 patients had significant myocardial damage or required emergency coronary bypass graft surgery during and after the angioplasty procedure.

Exercise capacity (Table II): One week after PTCA, the mean exercise time, peak workload, exercise heart rate and systolic blood pressure were significantly higher than values before PTCA (Fig. 8). The mean heart rate at rest and systolic blood pressure were not significantly different. In the 9 patients who had 6-month follow-up studies, except for a higher peak exercise systolic blood pressure, all exercise parameters were not significantly different between the 1-week and 6-month period after PTCA.

Exercise electrocardiography: Before PTCA, 12 of 20 patients had 1 mm or more of ST-segment depression during peak exercise (9 with 1 mm and 1 each with 1.5, 2 and 5 mm of ST depression) (Fig. 6). Only 1 of the 3 patients with electrocardiographic Q waves had further ST-segment depression (1 mm) during exercise.

One week after PTCA, exercise ST depression was abolished in 8 patients, unchanged in 2 and worsened in 2 (and increased from 1 to 2 mm of ST depression in both). The remaining patients had normal exercise electrocardiograms both before and 1 week after PTCA. Eleven patients had typical angina during exercise before PTCA; 7 of these also had positive (1-mm ST depression) exercise electrocardiographic changes. All but 1 patient (no. 17) became asymptomatic 1 week after PTCA. This patient also had worsening of his exercise electrocardiogram (an increment of ST-segment depression by 1 mm) (Table III).

Exercise radionuclide ventriculography: Data on exercise radionuclide ventriculography before and after PTCA were obtained in 17 patients. In these patients, LV ejection fraction at peak exercise increased significantly 1 week after PTCA (Table II, Fig. 9). This increase persisted in all except 1 patient studied at the 6-month follow-up. The mean LV ejection fraction decreased with exercise before PTCA but increased after PTCA. Regional wall motion showed significant im-

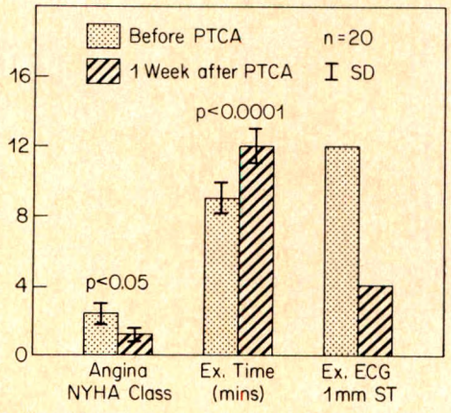

FIGURE 6. Mean New York Heart Association (NYHA) functional class, exercise (Ex.) duration and number of patients with abnormal ST-segment responses to exercise before and after angioplasty. ECG = electrocardiogram; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

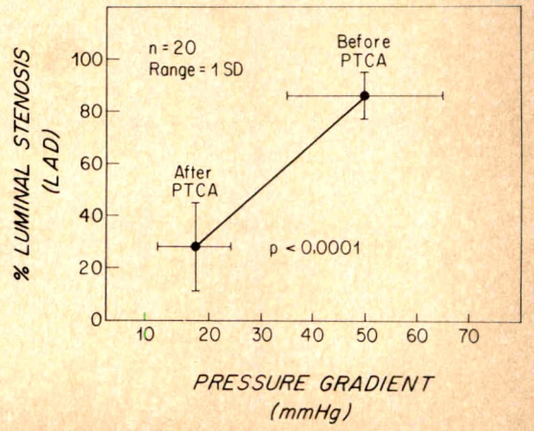

FIGURE 7. Percent luminal stenosis and pressure gradient before and after angioplasty. Abbreviation as in Figures 1 and 6.

TABLE III Changes in Exercise and Radionuclide Indexes One Week After Percutaneous Transluminal Coronary Angioplasty

Pt No.	Ex ECG	Ex Angina	Qualitative Tl-201			Quantitative Tl-201			Tl-201	Ex RVG	
			Dist.	Redist.	Lung	Dist.	Redist.	CI ($T^1/_2$)	Diff. Img.	Ex EF	Ex RWM
1	N	N+	A+	A+	N+	A+	A+	A+	N+	N+	N+
2	N	N	N+	N	N+	N+	N+	N+	N+	A+	N+
3	A	N+	A+	A+	N+	A+	N	A	N	N+	A+
4	N	N+	A	N	A+	A	N+	A+	N+	N+	A+
5	N	N	N+	N+	N+	A+	N+	N+	N+	N+	N+
6	A	N+	A+	N+	N+	A+	N+	N+	N+	N+	A+
7	N	N+	N	N	N	N	N	N+	N	N	N
8	A−	N+	A	N	N	A	A−	N	A	A−	N
9	N	N	A	A+	A+	A	A	A+	A	N	N
10	A	N	A+	A	N+	A+	A	N	A	N+	N+
11	N	N	N+	N+	N+	N+	N+	N+	N+	N+	N
12	N	N	N+	N+	N+	N+	A+	N	A+	N	N
13	N	N+	N+	N+	N	N+	N+	N+	N+	N+	N+
14	N	N+	N+	N+	N+	N+	N+	N+	N+	N	A
15	A	N	A−	N+	A	N	N+	N	N+	...	...
16	N	N	N+	N+	N+	A+	N+	N	N+	...	...
17	A−	A	A+	N	A+	A+	N	A	N	N	A
18	N	N+	N+	A	N+	A+	N+	N+	N+	N	N
19	N	N	A	A−	N	A−	N	A+	N	A−	A
20	N	N+	A+	N+	N+	A+	N	N+	N	...	...
						Totals					
N+	...	10	8	9	12	5	10	9	11	8	5
A+	...	...	6	3	3	9	2	4	1	1	3
N	14	9	1	5	4	2	5	5	5	6	6
A	4	1	4	2	1	3	2	2	3	0	3
A−	2	...	1	1	0	1	1	0	0	2	0

A = abnormal (status after percutaneous transluminal coronary angioplasty [PTCA]); CI = clearance rate of thallium-201; Diff. Img. = difference image; Dist. = distribution; ECG = electrocardiogram; EF = change in ejection fraction (5% increase in or decrease, or less than 5% change); Ex = exercise; N = normal (status after PTCA); Redist. = redistribution; RVG = radionuclide ventriculography; RWM = regional wall motion; Tl-201 = thallium-201; $T^1/_2$ = half-time; + = improved after PTCA; − = worse after PTCA; . . . = not done.

provement only in the septal segment during exercise. Abnormal wall motion (score 2.0 or less) in the septal region was present at peak exercise in 11 patients before PTCA. One week after PTCA, septal wall motion during peak exercise was completely normal in 6 of the 11 patients, was improved but remained hypokinetic in 2 and was unimproved in 3 (Table III). Regional wall motion in the remaining left ventricular segments did not change significantly after PTCA.

Exercise thallium-201 scan analysis: Exercise Tl-201 myocardial scintigraphy was obtained in all 20 patients before and 1 week after PTCA. Four of these patients had a second PTCA 2 to 8 months after the first, and in these patients exercise Tl-201 scans were repeated before and 1 week after the second PTCA as well. In addition, exercise Tl-201 scans were also performed in 5 other patients at 6 months after the initial PTCA.

Qualitative analysis of thallium-201 images (Table III): Visual interpretation of Tl-201 scans by 2

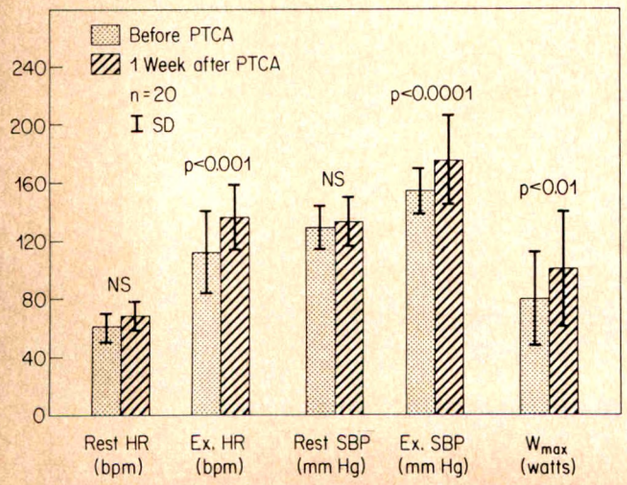

FIGURE 8. Exercise (Ex.) capacity before and after angioplasty: HR = heart rate; NS = not significant SBP = systolic blood pressure; W_{max} = peak exercise load in watts.

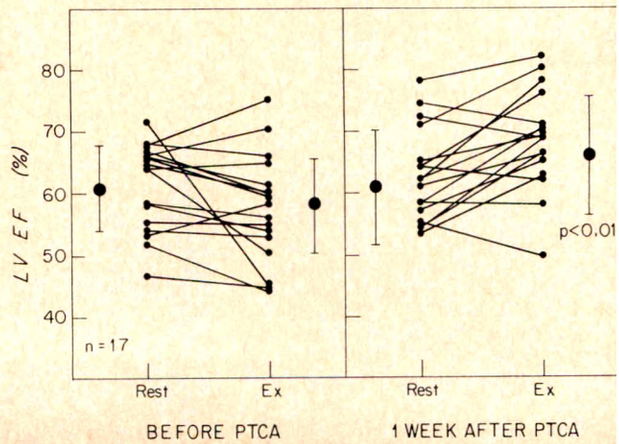

FIGURE 9. Left ventricular ejection fraction (LVEF) response to exercise (Ex.) before and 1 week after percutaneous transluminal coronary angioplasty (PTCA).

TABLE IV Changes in Quantitative Regional Thallium-201 Distribution in the Initial Images and Redistribution Between Delayed and Initial Images After Percutaneous Transluminal Coronary Angiography

	Quantitative Regional Tl-201			
	Initial Distribution (%)		Redistribution (%)	
LV Segment	Before PTCA	After PTCA	Before PTCA	After PTCA
Anterior				
Ant-basal(1)	64 ± 13	72 ± 9*	13 ± 14	9 ± 9
Ant-lat(2)	82 ± 17	94 ± 12†	11 ± 12	6 ± 7
Apical(3)	80 ± 14	91 ± 13*	6 ± 13	5 ± 8
Inf(4)	85 ± 12	90 ± 17	5 ± 13	9 ± 9
Inf-basal(5)	72 ± 11	74 ± 12	6 ± 13	6 ± 11
LAO 50°				
Post-basal(1)	70 ± 12	78 ± 19	14 ± 15	7 ± 10
Post-lat(2)	88 ± 7	94 ± 11	8 ± 11	3 ± 9
Apico-inf(3)	81 ± 13	92 ± 13†	16 ± 17	5 ± 12*
Septal(4)	66 ± 14	82 ± 17†	18 ± 17	8 ± 10*
Septal(5)	62 ± 15	73 ± 14†	17 ± 22	5 ± 11*
LAO 70°				
Inf-basal(1)	79 ± 8	86 ± 13*	4 ± 9	4 ± 9
Inferior(2)	89 ± 7	96 ± 10†	6 ± 9	3 ± 11
Apical(3)	73 ± 13	90 ± 17‡	8 ± 13	1 ± 9
Anterior(4)	71 ± 12	92 ± 16§	8 ± 16	1 ± 7
Ant-basal(5)	72 ± 13	84 ± 18*	15 ± 15	3 ± 13*

* $p < 0.05$ compared with previous value; † $p < 0.01$ compared with previous value; ‡ $p < 0.0001$ compared with previous value; § $p < 0.001$ compared with previous value.

Ant-basal = anterobasal; Ant-lat = anterolateral; Apico-inf = aspicoinferior; Inf-basal = inferobasal; LAO = left anterior oblique; LV = left ventricular; Post-basal = posterobasal; Post-lat = posterolateral; PTCA = percutaneous transluminal coronary angioplasty; Tl = thallium-201.

observers showed improvement in the initial Tl-201 images after exercise in 14 of the 20 patients 1 week after PTCA. Of these, 8 were assessed as totally normal and 6 had residual abnormalities on their Tl-201 scans. Significant areas of Tl-201 redistribution were abolished in 9 patients and improved in 3 after PTCA. In 5 patients, Tl-201 distribution remained inhomogeneous in the LAD territories and was unimproved by PTCA. Thallium-201 uptake in the lungs in the initial images after exercise was clearly qualitatively abnormal in 10 patients and borderline abnormal in 6 patients before PTCA. After PTCA, the lung uptake of Tl-201 was completely normal in 13 patients and improved but still abnormal in 3 patients.

Quantitative analysis of thallium-201 images (Table IV): When the initial postexercise images obtained before and after PTCA were analyzed as serial images using the new computer program described, the mean normalized regional Tl-201 activity in the myocardial regions supplied by the dilated LAD increased significantly 1 week after PTCA. The mean Tl-201 uptake in the apical segments in all these views also increased significantly. In the anterior and LAO 50° views, the normalized Tl-201 uptake in the nondilated segment did not show significant changes after PTCA. Differences in normalized regional Tl-201 activity between the delayed and early images after exercise, representing redistribution of Tl-201 in ischemic but viable segments supplied by the dilated LAD, showed corresponding significant diminution 1 week after PTCA. The decrease in Tl-201 redistribution after exercise occurred in the septal and apicoinferior segments (segments 3, 4 and 5) in the 50° LAO view and in the anterobasal segment (segment 5) 70° LAO view. Changes in Tl-201 redistribution in the other segments were not statistically significant (Table IV).

After PTCA, 11 patients who had Tl-201 redistribution before PTCA, depicted by the difference images between the delayed and initial images, showed improvement in these segments indicated by disappearance or diminution of the intensity color-coded abnormal regions (Fig. 5, Table III).

No significant correlation was found between either the degree of improvement in initial regional Tl-201 uptake or the amount of Tl-201 redistribution between delayed and initial images, and either the change in percent luminal stenosis or the change in pressure gradient across the LAD lesion before and after successful PTCA.

Regional thallium-201 clearance rate: Patients with 1-vessel CAD present a unique model to study myocardial Tl-201 kinetics. Table V shows the difference in myocardial Tl-201 clearance in the segments supplied by the diseased LAD in the anterior view compared with that in segments supplied by nondiseased coronary arteries. Before PTCA, mean Tl-201 counts increased instead of decreased between the initial and intermediate images in the LV segments supplied by the stenosed LAD. This increase, however, was not statistically significant in this group of 20 patients. In the normal inferior segments, this increase in regional Tl-201 activity between the initial and intermediate images was absent. One week after PTCA, the myocardial clearance of Tl-201 in the segments perfused by

TABLE V Changes in Quantitative Regional Thallium-201 Count-Activity and Clearance Rate in the Initial, Intermediate and Delayed Postexercise Images of the Anterior View After Percutaneous Transluminal Coronary Angioplasty

LV Segment	Regional Tl-201 Counts (Initial Postexercise Image)		Regional Tl-201 Cl ($t^1/_2$) (hours)	
	Before PTCA	After PTCA	Before PTCA	After PTCA
SEG 1 (ini.)	66 ± 10	69 ± 8	9 ± 4	4 ± 3*
SEG 1 (int.)	69 ± 11	66 ± 10		
SEG 1 (del.)	52 ± 13	43 ± 14		
SEG 2 (ini.)	85 ± 11	90 ± 7	12 ± 12	4 ± 2†
SEG 2 (int.)	90 ± 11	86 ± 12		
SEG 2 (del.)	64 ± 14	53 ± 18		
SEG 3 (ini.)	81 ± 12	85 ± 10	7 ± 5	4 ± 4
SEG 3 (int.)	81 ± 10	78 ± 14		
SEG 3 (del.)	57 ± 12	48 ± 17		
SEG 4 (ini.)	83 ± 9	82 ± 13	6 ± 5	5 ± 6
SEG 4 (int.)	82 ± 9	78 ± 14		
SEG 4 (del.)	58 ± 13	47 ± 16		
SEG 5 (ini.)	71 ± 9	67 ± 11	5 ± 2	7 ± 10
SEG 5 (int.)	67 ± 10	63 ± 12		
SEG 5 (del.)	45 ± 11	38 ± 13		

* $p < 0.001$; † $p < 0.01$.
Cl = clearance; del. = delayed; ini. = initial; SEG = segment; other abbreviations as in Tables III and IV.

the dilated LAD resembled that of segments with normal coronary flow. Regional Tl-201 clearance rate (expressed as mean effective $t^1/_2$ [hours]) was abnormally slow in the LAD territories before PTCA and improved significantly after PTCA (Table V).

Comparison of qualitative vs quantitive analysis of thallium-201 scans: Fourteen of the 20 patients had improvement in their Tl-201 scans after PTCA, assessed both qualitatively and quantitatively (Table III). In 1 patient (no. 15), visual interpretation of Tl-201 distribution was assessed as normal before but abnormal after PTCA, whereas quantitation of Tl-201 distribution was normal both before and after PTCA.

Quantitatively generated difference images had the same sensitivity in detecting improvement in regional Tl-201 redistribution (12 of 20) compared with visual and quantitative analysis (Table III). Quantitative analysis of regional Tl-201 distribution in the initial postexercise images, however, showed a greater sensitivity in detecting improved Tl-201 uptake in segments supplied by the dilated LAD (Table VI).

TABLE VI Comparison of Quantitative Versus Qualitative Analysis of Changes in Regional Thallium-201 Distribution After Successful Percutaneous Transluminal Coronary Angioplasty*

LV Segments	Qualitative			Quantitative		
	I	U	W	I	U	W
Ant-lat (ant)	6	12	2	9	10	1
Septal (LAO 50°)	11	5	4	11	6	3
Ant (LAO 70°)	12	7	1	12	6	2
Apical (3 views)	6	12	2	7	10	3
Inferior (ant)	2	16	2	6	9	5
Inferior (LAO 50°)	2	16	2	3	12	5
Inferior (LAO 70°)	0	19	1	2	14	4

* Data refers to number of patients.
I = improved; U = unchanged; W = worsen; other abbreviations as in Table IV.

Six months after percutaneous transluminal coronary angioplasty: In the 9 patients who underwent repeat noninvasive study at 6 months after PTCA, 5 patients (nos. 1, 2, 4, 5 and 7—group A) were asymptomatic at that time. Four patients (nos. 3, 10, 14 and 17—group B) required a second PTCA to the same lesion between 2 to 8 months after the first PTCA because of recurrent angina and restenosis of the original lesion. When changes in regional Tl-201 distribution, redistribution and clearance before and after PTCA were compared in group A and group B patients, greater improvement at 1 week after PTCA was present in group A compared with that in group B patients. These changes did not reach a statistically significant level ($p = 0.07$) in this small number of patients (Table VII).

Discussion

The present study objectively documents the beneficial effects of PTCA on clinical, angiographic and hemodynamic measurements, and on regional myocardial perfusion and function. This study also demonstrates the value of a new computer approach to

TABLE VII Differences in Regional Thallium-201 Distribution in the Left Anterior Descending Coronary Artery Territories at Six-Month Follow-Up in Patients Not Requiring (Group A) and Requiring (Group B) Repeat Percutaneous Transluminal Coronary Angioplasty

LV Segment		Group A (n = 5)	Group B (n = 4)
Septal (LAO 50°)	Before PTCA	67 ± 22	75 ± 4
	1 week after	98 ± 16	71 ± 17
	2–8 mo. after	82 ± 9	65 ± 13
Anterior (LAO 70°)	Before PTCA	66 ± 20	75 ± 13
	1 week after	89 ± 21	86 ± 11
	2–8 mo. after	86 ± 14	67 ± 17

Abbreviations as in Table IV.

quantitate changes in regional myocardial perfusion after PTCA from exercise Tl-201 scintigraphic scans. The approach allows objective assessment of the early and long-term effects of PTCA on regional myocardial perfusion. Using the new quantitative technique, the findings at 1 week after PTCA indicated improvement in regional Tl-201 uptake in the ventricular segments supplied by the dilated coronary artery.

Improvement in both regional myocardial perfusion and function after PTCA has been reported by other workers[5–10,16] However, the new approach to quantitate changes in regional Tl-201 distribution presents several unique features not previously described. First, the automatic realignment of serial LV Tl-201 images enables direct comparison of the same anatomic regions of the heart in an objective manner. Second, this method's determination of Tl-201 activity profile curves does not depend on the assumption of a geometric center, which is difficult, if not impossible, to locate accurately in a dynamically contracting heart. Third, this method estimates regional myocardial Tl-201 activity in a transmural fashion from a 3 pixel-wide myocardial band. This is in contrast to other reported methods of quantitating regional Tl-201 distribution from circumferential profiles using peak activity in a single pixel.[17–19] In addition to the assessment of regional Tl-201 distribution, quantitative assessment of regional Tl-201 redistribution between the initial postexercise and delayed images is also an important feature. The presence of Tl-201 redistribution over time indicates ischemic but viable myocardium.[20] The ability to quantitate this redistribution by the present technique is particularly useful in the clinical evaluation of patients before PTCA in order to detect jeopardized by viable myocardium.

The data in the present study suggests a difference in the degree of improvement in postexercise regional Tl-201 distribution in patients whose lesions are likely to restenose compared with those destined to remain patent. In the 5 patients who remained clinically well at 6 months after successful PTCA, the increase in regional Tl-201 distribution was greater than in those who did not do as well clinically. The beneficial effects of PTCA on regional myocardial perfusion persisted at 6 months in patients who remained asymptomatic. However, in 4 patients who required repeat PTCA within 2 to 8 months after the initial PTCA, because of the recurrence of troublesome symptoms and coronary restenosis at the same site, the improvement in Tl-201 distribution 1 week after the initial PTCA was not as great as that for patients who remained clinically well at the 6-month follow-up. Although the differences in the degree of improvement in regional Tl-201 activity in these 2 groups did not reach a statistically significant level, with more patients followed up over a longer period, this difference in regional Tl-201 uptake after PTCA may be found to be an indicator of patients who might require closer clinical supervision or earlier repeat angiography, or both.

This group of 20 patients with isolated LAD CAD presents a unique model for studying the myocardial clearance of Tl-201 under normal and ischemic conditions. It has been well documented that the Tl-201 clearance rate from ischemic myocardium is slower than that from normally perfused myocardium.[21–24] In the present study group, the myocardial Tl-201 did not washout significantly between the initial and 30-minute imaging times in the diseased segments before PTCA. After PTCA, the regional Tl-201 counts decreased between the initial and 30-minute imaging times in both the LAD supplied and the normally perfused segments. The post-intermediate image clearance rate was also restored to normal in the previously jeopardized segments after PTCA. Thus, the Tl-201 clearance rate appears to be an additional sensitive index for assessing reversal of ischemia after PTCA.

Of the 17 patients who had exercise radionuclide ventriculography before and after PTCA, 8 patients who had an exercise-induced decrease in ejection fraction before PTCA either had a significant increase or a flat ejection fraction response to exercise after PTCA. Regional wall motion, most notably in the septum, was also improved in several patients after PTCA. These findings of improved global and regional LV function after PTCA closely resemble those results reported after successful coronary artery bypass graft surgery.[25–27]

In conclusion, we have objectively demonstrated the immediate and long-term beneficial effects of PTCA on regional myocardial perfusion, overall clinical status and myocardial function in patients with 1-vessel LAD CAD. The noninvasive technique used in the present study may have wider clinical applications, such as the assessment of changes in regional coronary perfusion and myocardial viability after mechanical or pharmacologic intervention in the setting of acute myocardial infarction.

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Early Detection of Restenosis After Successful Percutaneous Transluminal Coronary Angioplasty by Exercise-Redistribution Thallium Scintigraphy

WILLIAM WIJNS, MD, PATRICK W. SERRUYS, MD, JOHAN H.C. REIBER, PhD, PIM J. de FEYTER, MD, MARCEL van den BRAND, MD, MAARTEN L. SIMOONS, MD, and PAUL G. HUGENHOLTZ, MD, *With the statistical assistance of* JAN G.P. TIJSSEN

The value of exercise testing and thallium scintigraphy in predicting recurrence of angina pectoris and restenosis after a primary successful transluminal coronary angioplasty (PTCA) was prospectively evaluated. In 89 patients, a symptom-limited exercise electrocardiogram (ECG) and thallium scintigraphy were performed 4 weeks after they had undergone successful PTCA. Thereafter, the patients were followed for 6.4 ± 2.5 months (mean ± standard deviation) or until recurrence of angina. They all underwent a repeat coronary angiography at 6 months or earlier if symptoms recurred. PTCA was considered successful if the patients had no symptoms and if the stenosis was reduced to less than 50% of the luminal diameter. Restenosis was defined as an increase of the stenosis to more than 50% luminal diameter. The ability of the thallium scintigram (presence of a reversible defect) to predict recurrence of angina was 66%, vs 38% for the exercise ECG (ST-segment depression or angina at peak workload). Restenosis was predicted in 74% of patients by thallium scintigraphy, but only in 50% of patients by the exercise ECG. Thus, thallium scintigraphy was highly predictive but the exercise ECG was not ($p < 0.005$). These results suggest that restenosis had occurred to some extent already at 4 weeks after the PTCA in most patients in whom it was going to occur.

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Restenosis after primary successful percutaneous transluminal coronary angioplasty (PTCA) occurs in 19 to 36% of patients within the first 6 months after the procedure.[1–5] This restenosis may manifest itself by changes in the patient's clinical status and may be detected by noninvasive diagnostic tests or by coronary angiography. Scholl[2] and Hirzel[6] and their co-workers showed that an abnormal response on the exercise electrocardiogram (ECG) and a myocardial perfusion defect on the thallium scintigram is associated with angiographically documented restenosis of the dilated vessel or is a sign of the presence of additional disease. The present study was performed to determine the value of early noninvasive testing in the prediction of restenosis and recurrence of symptoms. The study patients had undergone technically successful PTCA, which resulted in a "complete" anatomic correction. They were all free of angina pectoris up to the time of exercise electrocardiography and thallium scintigraphy, which were performed a median of 4 weeks after PTCA. Follow-up data regarding subsequent recurrence of symptoms and repeat coronary angiography a median of 6 months after the procedure were compared in a prospective manner with the noninvasive test results obtained at 4 weeks.

From the Thoraxcenter, Erasmus University and University Hospital Dijkzigt, Rotterdam, The Netherlands. Manuscript received June 27, 1984; revised manuscript received October 15, 1984, accepted October 16, 1984.

Address for reprints: Patrick W. Serruys, MD, Catheterization Laboratory, Thoraxcenter, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

Methods

Between September 1980 and September 1983, 296 consecutive first PTCA procedures for stable or unstable angina pectoris were attempted at the Thoraxcenter; 221 were primary successes. The 162 patients from our own institution were asked to cooperate with a follow-up protocol, which included an exercise electrocardiogram and thallium scintigram 4 to 6 weeks after the procedure, a visit to the outpatient clinic at 2-month intervals and a repeat angiogram at 6 to 8 months. The 59 patients referred from institutions in other cities were excluded. One hundred twenty patients met the inclusion criteria for the present study: "complete" anatomic correction,

TABLE I Characteristics of the Angioplasty Procedure

		Group 1 Restenosis* (n = 35)		Group 2 Long-Term Success (n = 54)
Dilated vessel (n = 93)	LAD	25		34
	LCX	6		3
	RCA	5		19
	Bypass	1		0
% diameter stenosis	Pre	66 ± 15	NS	62 ± 11
	Post	33 ± 12	NS	31 ± 13
	Late	62 ± 14		31 ± 13
Pressure gradient	Before	0.64 ± 0.16 (33)	NS	0.61 ± 0.13 (55)
	After	0.19 ± 0.11 (35)	NS	0.16 ± 0.10 (55)

The translesional pressure gradient is normalized for the mean aortic pressure; numbers under parentheses refer to the number of available measurements. * Stenosis more than 50% in luminal diameter at repeat angiography.

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; NS = not significant; RCA = right coronary artery.

TABLE II Exercise Test Results and Recurrence of Symptoms During Follow-Up

	Group 1 Restenosis (n = 35)		Group 2 Long-Term Success (n = 54)
Weeks after PTCA (range)	4.7 ± 2.3 (2–11)	NS	4.7 ± 1.7 (2–8)
Maximal workload (% of predicted)	96 ± 13	NS	90 ± 16
Maximal heart rate	140 ± 28	NS	149 ± 22
Abnormal exercise ECG	13		13
Angina during test	1		3
ST depression >0.1 mV	11		10
Both	1		0
Abnormal scintigram	26		9
Recurrent angina	23		6
New myocardial infarction	0		0

ECG = electrocardiogram; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

i.e., no significant residual coronary obstructions after PTCA; absence of angina until the time of exercise testing; and ability to complete the exercise test. Thirty-one patients refused to undergo repeat coronary angiography. This report is thus based on the prospective evaluations of 89 patients, 74 men and 15 women. A single stenosis was dilated in 85 patients and 2 stenoses were dilated in 4 patients. The dilated vessel was the left anterior descending artery in 59 patients, the left circumflex in 9, the right coronary artery in 24 and the distal anastomotic site of a saphenous vein bypass graft on the left anterior descending coronary artery in 1 patient. PTCA was performed according to the technique of Gruentzig,[1] with Schneider equipment through a femoral route. Details regarding the procedure used in our laboratory were described previously.[7,8] The PTCA procedure was considered successful when the residual stenosis was less than 50% in diameter with a good run off and filling of the distal vessel at angiography. In the 91 stenoses with satisfactory recordings, the residual pressure gradient (normalized for the mean aortic pressure) was less than 0.20 in 63 cases and less than 0.40 in 25 cases.

In an attempt to reduce the restenosis rate,[3,5] all patients received nifedipine, 10 mg every 2 hours for the first 8 hours after the procedure and received maintenance therapy on salicylic acid, 500 mg/day, and nifedipine, 10 mg 3 to 6 times daily, until repeat angiography was performed. Beta-blocking agents were stopped unless the patient had hypertension. Repeat angiography was performed 7.0 ± 2.3 months (mean ± standard deviation) after PTCA in the patients who remained asymptomatic and 4.9 ± 2.3 months after PTCA in patients who had recurrent angina during follow-up. Coronary angiography was performed in multiple views (including hemiaxial views for the left coronary artery) and were interpreted visually without knowledge of the initial noninvasive test results. The clinical definition of restenosis was an increase of the diameter stenosis of the dilated lesion above the 50% level. In addition, quantitative analysis of the dilated stenosis was obtained in the same angiographic projection for each angiogram by means of our computer-based coronary angiographic analysis system.[9] Based on these accurate and more objective measurements of stenosis severity,[10] the definition of restenosis used by the National Heart, Lung, and Blood Institute (NHLBI) registry[4] was applied as well, i.e., an increase in stenosis of at least 30% from the immediate post-PTCA result or the loss of at least half the initial gain in diameter.

The exercise studies were performed 4.7 ± 1.9 weeks after PTCA. The subjects performed a symptom-limited exercise test on the bicycle ergometer with stepwise increments of 20 W/min. The 3 orthogonal leads XYZ of the Frank lead system were recorded and analyzed as previously described.[11] The reported sensitivity and specificity for the diagnosis of significant coronary disease were 85% and 90%, respectively. Horizontal ST depression of 0.1 mV or greater and typical angina during exercise were considered as abnormal (or positive) responses. One minute before peak exercise, thallium, 1.5 mCi, was injected intravenously. Imaging was started 5 minutes later in 3 views: anterior, left anterior oblique 45° and 65°. Static planar images (500 kcounts full field, zoom 2 ×) were obtained after exercise and 4 hours later with a Searle Phogamma V camera. The scintigraphic images were processed on a DEC gamma-11 system with a quantification procedure developed at our institution.[12] The late image was corrected for acquisition time differences with respect to the early image. The exercise and redistribution images were registered on the basis of the detected positions of point sources taped to the patient's chest. After automated left ventricular contour detection[13] and interpolative background correction,[14] circumferential profiles were computed at 6° intervals. The profiles of the early and late images were normalized for the maximal value in the early image (100%) excluding the outflow tract of the left ventricle. The analog Polaroid® images from the gamma camera, the processed images and the circumferential profiles were analyzed prospectively on a routine basis by 3 experienced observers without knowledge of the angiographic data. The thallium uptake in a total of 11 segments was scored both in the postexercise and late images on a 5-point scale: 0 = no thallium uptake; 1 = severely abnormal; 2 = definitely abnormal; 3 = doubtfully abnormal; and 4 = normal. The following segments were defined: posteroseptal, inferior, apical and anterolateral in the anterior view; anteroseptal, apical and posterolateral in the left anterior oblique 45° view; and anterior, apical, inferior and posterior in the left anterior oblique 65° view. The scores of all segments were summed per patient and the difference between late and early postexercise sums was taken as a measure of the amount of redistribution. An increase in thallium uptake score of 2 points or more between postexercise and late images was taken as the cutoff between normal (absence of exercise-induced ischemia) and abnormal (presence of exercise induced ischemia) scintigrams. Persistent defects without redistribution were considered to represent scars

TABLE III Positive and Negative Predictive Values of the Noninvasive Tests

	Restenosis					
	50% Diameter		NHLBI Criteria*		Recurrent Angina	
	Present (n = 35)	Absent (n = 54)	Present (n = 37)	Absent (n = 52)	Present (n = 29)	Absent (n = 60)
Predictive value	+	−	+	−	+	−
Exercise ECG ST segment	55 (12/22)	66 (44/67)	55 (12/22)	63 (42/67)	32 (7/22)	67 (45/67)
ST and/or AP	50 (13/26)	65 (41/63)	54 (14/26)	63 (40/63)	38 (10/26)	70 (44/63)
Thallium scintigraphy	74 (26/35)	83 (45/54)	74 (26/35)	80 (43/54)	66 (23/35)	89 (48/54)

Positive (+) and negative (−) predictive values of respectively abnormal and normal tests are percentages.

* An increase in stenosis of 30% or more from the immediate post-PTCA result and/or the loss of at least half the initial gain in diameter.

AP = angina pectoris; ECG = electrocardiogram; NHLBI = National Heart, Lung, and Blood Institute.

without exercise-induced ischemia. With this analysis, the previously reported sensitivity and specificity for the diagnosis of significant coronary artery obstructions were 80 and 88%, respectively.[12] The patients were followed up in the outpatient clinic until occurrence of typical angina pectoris or a new myocardial infarction. The follow-up duration was 6.4 ± 2.5 months. No patient died during this period.

Results are presented as mean ± standard deviation. The *t* test for paired or unpaired data was used whenever appropriate. The positive predictive value for restenosis (or recurrent angina) was calculated as the frequency of restenosis (or recurrent angina) in those with abnormal test results. The negative predictive value for the absence of restenosis (or recurrent angina) was calculated as the frequency of long-term success in those with normal test results. Differences between correct and incorrect classifications by exercise ECG vs thallium were evaluated by the McNemar test.

Results

The characteristics of the PTCA procedure are listed in Table I for 2 groups: patients with restenosis of the dilated vessel, i.e., diameter stenosis at repeat angiography more than 50% (n = 35), and patients with long-term success (n = 54). There was no significant difference between these 2 groups in the pressure gradient across the stenosis either before or after PTCA. The exercise test results and the recurrence of symptoms during the follow-up are summarized for both groups in Table II. The mean timing of exercise testing after PTCA and the resultant maximal workloads and heart rates achieved were similar for both groups. Ninety-two percent of the patients reached 80% of their predicted maximal workload. An abnormal exercise ECG was observed in 26 patients: 21 had ST-segment depression, 4 had angina at peak workload and 1 patient had both.

Exercise-induced ischemia as assessed by the thallium redistribution was observed in 35 patients. During the follow-up, angina recurred in 29 patients. No patient had a new myocardial infarction in the territory of the dilated vessel. The positive and negative predictive values of each single test are shown in Table III. Thallium was superior to the exercise ECG both for the prediction of recurrent stenosis and recurrent angina (both $p < 0.005$). The predictive value for recurrent stenosis of the 4 combinations of test results is shown in Figure 1. An abnormal scintigraphic response was associated with a high incidence of restenosis, which was not influenced by the result of the exercise ECG: 71% of restenoses when both tests were abnormal vs 76% when tests were discordant. Conversely, a normal scintigraphic response was associated with a low incidence of restenosis, which was also not influenced by the result of the exercise ECG: 14% of restenosis when both tests were normal and 25% when tests were discordant.

The value of combined noninvasive test results for the prediction of recurrent angina is shown in Figure 2. Angina recurred in 64% of patients with both tests abnormal and in 67% of patients with only thallium abnormal. In the presence of a normal scintigraphic response, the recurrent angina was about 10%, regardless of the result of the response on the exercise ECG.

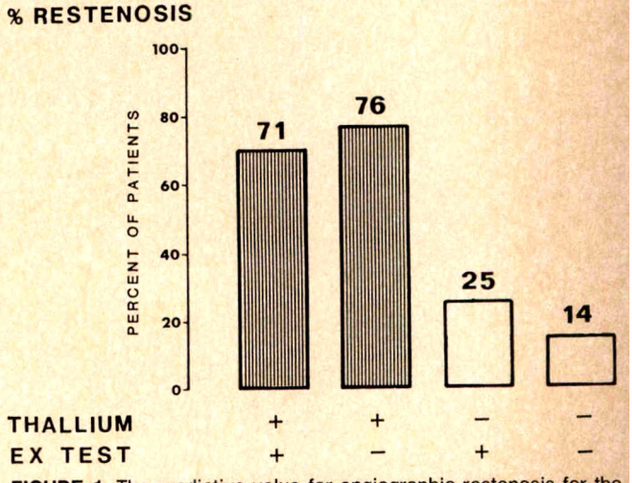

FIGURE 1. The predictive value for angiographic restenosis for the possible combinations of noninvasive test results: (+) = abnormal test and (−) = normal test; EX TEST = exercise electrocardiogram. **Shaded columns** represent the patients with abnormal scintigraphic responses. Both test results were abnormal in 14 and normal in 42 patients; only thallium was abnormal in 21 and only exercise ECG in 12 patients.

By the NHLBI definition of restenosis based on the quantitative analysis of the angiograms, only 6 patients were categorized in another group; 37 had restenosis by these criteria. The predictive value of the noninvasive tests was not significantly different: 54% restenosis when the exercise ECG was abnormal vs 74% restenosis when the scintigram was abnormal (Table III).

Discussion

The present report demonstrates that early assessment of myocardial perfusion by exercise thallium scintigraphy has a high predictive value for restenosis and recurrence of angina in patients who underwent a technically satisfactory PTCA. Previous studies[2,6,15–17] assessing the results of PTCA by noninvasive tests have focused on the reversibility of the ischemic changes after a successful procedure and on their induction at the time of recurrence. However, more recently, DePuey et al[18] reported that failure to increase ejection fraction or the development of a new regional wall motion abnormality during exercise radionuclide ventriculography early after PTCA predicted restenosis at 4 to 12 months in 73% of 41 patients. Their findings and those of the present study suggest that restenosis had occurred to some extent already at 4 weeks in most patients in whom it was documented later. This observation raises speculations about the underlying mechanism of restenosis after dilatation. Fibrocellular proliferations as a reparative response to coronary wall laceration has been described in necropsy studies[19] and may represent the pathologic substrate of early restenosis. In analogy with aortic dissection, exposure of vascular smooth muscle cells to blood may trigger an exuberant tissue reaction, leading to obliteration of the false channel and eventually of the functional lumen. Preliminary data[20] from experimental angioplasty in pigs suggest that balloon dilatation is a potent stimulus to early platelet deposition and subsequent intimal hyperplasia. In this model, the reparative process was observed as early as 2 weeks after the procedure. If present in patients, such ongoing processes may have induced the observed perfusion abnormalities. Since only successful cases were included and the decrease in stenosis severity and in the transstenotic pressure gradient were comparable in patients with restenosis and long-term success, there is no evidence that recurrence occurred predominantly in patients in whom the dilatation was incomplete. In this study, the high predictive value of the perfusion scintigram contrasts with the poor predictive value of the exercise electrocardiographic response, especially for the prediction of restenosis.

This could be explained by a lower sensitivity of the exercise ECG compared with thallium scintigraphy in the detection of moderate coronary artery narrowing. The combination of a normal exercise ECG with a reversible thallium perfusion abnormality could be an early indicator of the presence of a noncritical stenosis, still insufficient to induce ST-segment depression during exercise.[21] Indeed, 66% of the patients with an initially abnormal scintigram became symptomatic at a later stage during the follow-up period.

The problem of defining restenosis is not trivial. Applying the stringent criteria of the NHLBI registry to visual estimations of stenosis severity has major limitations, due to the large intra- and interobserver differences in interpretation, especially for stenoses between 20 and 80%.[22] Therefore, the stenoses were analyzed by computerized edge detection. Although this method may not be optimal after angioplasty,[9] it provides an objective and quantitative measurement, avoiding unintentional bias in reading the angiograms. This complex definition of restenosis resulted however in similar findings as the usual clinical approach based in the presence or the absence of a hemodynamically significant stenosis (>50% luminal diameter). By this clinical definition, restenosis of the dilated artery was observed in 39% and recurrent angina pectoris in 33% of the patients.

The true incidence of recurrence is probably lower because most of the patients who refused to undergo repeat angiography were asymptomatic. The patient population is thus biased in favor of those with recurrent stenosis. The clinical implication of these findings for the routine management of patients who undergo PTCA remains to be established. Certainly we share with DePuey et al[18] the conclusion that an abnormal noninvasive test early after PTCA in an asymptomatic patient is an indication for close clinical monitoring in view of the high chance of recurrence of symptoms. We believe that decisions to perform repeat angiography, followed by a redilatation when restenosis is found, should primarily be based on the severity of angina rather than on the results of the testing procedure. This is analogous to the issue of bypass surgery for documented coronary artery disease in asymptomatic patients, particularly since no benefit of surgical intervention over pharmacologic treatment was shown in mildly or nonsymptomatic patients.[23] Until the outcome

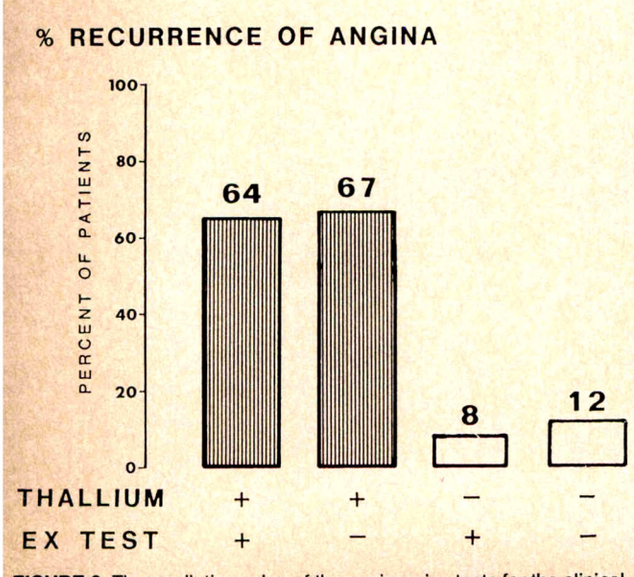

FIGURE 2. The predictive value of the noninvasive tests for the clinical endpoint (recurrent angina); other abbreviations as in Figure 1.

of prophylactic PTCA is studied, the procedural complications and incomplete success rates militate against performing PTCA when diagnostic testing reveals restenosis in the absence of symptoms.

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Comparison of Preoperative, Operative and Postoperative Variables in Asymptomatic or Minimally Symptomatic Patients to Severely Symptomatic Patients Three Years After Coronary Artery Bypass Grafting: Analysis of 423 Patients

PIM J. de FEYTER, MD, PATRICK W. SERRUYS, MD, RONALD W. BROWER, PhD, MARCEL van den BRAND, MD, HARALD J. ten KATEN, BSc, PAUL G. HUGENHOLTZ, MD, and EGBERT BOS MD

During a follow-up period of 3 years, among a consecutive series of 423 patients who gave informed consent for recatheterization both 1 and 3 years after coronary artery bypass grafting, the incidence of severely symptomatic patients with New York Heart Association class III or IV was 19% (79 of 423). The predictive value of approximately 80 clinical, angiographic and perioperative variables was too low to be of clinical value. Adverse clinical outcome was associated with a high closure rate of the grafts. Forty-six percent of the patients could not undergo reoperation because of unsuitable coronary anatomy. With intensive medical therapy half of these patients improved to functional class I or II, while of those patients who were reoperable 32% improved to class I or II with intensive pharmacologic treatment instead of reoperation. The nonresponders underwent reoperation, which resulted in improvement of symptoms to functional class I or II in most (83%). (Am J Cardiol 1985;55:362–366)

In this report we focus on patients who became severely symptomatic after coronary artery bypass grafting (CABG) during 3 years of follow-up. The following questions were posed: What is their incidence? Can an adverse postoperative outcome be predicted from preoperative or perioperative variables? What are the explanatory factors for this adverse outcome? What is the reoperability rate, how were these patients actually managed and what was their clinical outcome?

Methods

From January 1976 to December 1979, a consecutive series of 637 patients underwent CABG at the Thoraxcenter, Rotterdam. All patients had symptoms before operation despite adequate medical treatment. The complaints were stable or unstable angina. Patients with coexisting valvular or congenital heart disease, those who had undergone left ventricular (LV) aneurysmectomy, surgery for dysrhythmias, and those with a life expectancy of less than 5 years because of other serious disease were excluded. Four hundred twenty-three patients (66%) agreed to undergo recatheterization at 1 and 3 years after operation, irrespective of their postoperative complaints. These patients constitute the study population. Before CABG, 34% of the patients did not agree to undergo 2 postoperative catheterizations. On the basis of clinical data (age, sex, severity of symptoms and previous myocardial infarction [MI]) and preoperative angiographic data (severity and extent of coronary artery disease (CAD) and LV function), both groups (no informed consent vs informed consent) were comparable.

Of the 423 patients who formed the study population, 3 died during operation. During a follow-up of 3 years, 79 patients have become severely symptomatic and 341 patients have had no or mild symptoms. (Fig. 1).

Follow-up and management: All patients were seen every 6 months in the outpatient department over the 3-year period. Severe symptoms (persistent or recurrent) were defined as angina pectoris of New York Heart Association (NYHA) functional class III or IV severity. All but 1 of the 79 severely symptomatic patients could be evaluated with angiography. Reoperability was assessed in joint discussion between the

From the Thoraxcenter, Erasmus University, and Interuniversity Cardiology Institute, Rotterdam, The Netherlands. Manuscript received July 18, 1984; revised manuscript received October 24, 1984, accepted October 25, 1984.

Address for reprints: Pim J. de Feyter, MD, Dijkzigt ziekenhuis, Thoraxcentrum Bd428, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

cardiac surgeons and cardiologists. After assessment of reoperability, all severely symptomatic patients were initially treated with intense pharmacologic therapy. The patients who had no adequate response to this treatment and those who desired a reoperation (a minority) underwent reoperation. Intensive pharmacologic therapy consisted of nitrates (short- and long-acting) and β-adrenergic agents, inasmuch as calcium antagonists were not available before 1979.

Of the 341 patients with no or mild symptoms despite initial agreement for recatheterization, 276 actually underwent this procedure at 1 year and 158 at 3 years. The patients who did not undergo recatheterization refused upon reconsideration. Clinically available information indicated that the patients who refused recatheterization did not differ from those who consented.

Coronary angiography: Selective coronary angiography was performed in multiple projections including hemiaxial views. The degree of luminal narrowing was coded according to the guidelines of the American Heart Association.[1] The degree of luminal narrowing was assessed visually and scored as less than 50%, 50 to 89%, 90 to 99%, and 100%. The bypass grafts were infused selectively with contrast medium to establish patency.

The severity of the underlying CAD before and after CABG was quantified by the coronary score system developed by Leaman and Brower and their co-workers.[2,3] This coronary score represents the combined effect of the disease in a segment of the coronary artery weighted according to the significance of that vessel. A score of 0 would indicate no obstructive disease, whereas the higher the score, the greater the severity of disease.

In deriving the postoperative coronary score, a vessel segment supplied by a graft was considered to take over the disease factor, if any, of the graft, provided there was no other total occlusion distal to this segment and proximal to the graft anastomose. This postoperative score represents remaining CAD, taking into account disease in the native system as well as closure of grafts.

From this principle, 2 additional postoperative scores could be derived: the coronary score corrected for CABG immediately after surgery and during follow-up, assuming all grafts patent and normal, representing remaining disease in the native coronary system that could not be effectively bypassed, and the coronary score corrected for CABG assuming all grafts closed (or not placed), representing severity of disease in the total native coronary system during follow-up.

Statistical analysis: Univariate statistical analysis was performed using either the chi-square test or Student t test when appropriate using double-sided distributions. Multivariate discriminant function stepdown function analysis was performed with program P7M of the BMDP statistical package.

Results

Characteristics of the population: Of the 423 patients, 93% were men; mean age was 51.6 ± 7.1 years. Sixty-eight percent had a previous MI. Sixteen percent of the patients had 1-vessel, 27% had 2-vessel, 50% had 3-vessel and 6% left main CAD. Sixty percent of the patients had an ejection fraction greater than 0.50, 24% between 0.30 and 0.50, and 2% less than 0.30; the ejection fraction was unknown in 13%. The perioperative mortality was 0.7% (3 of 423 patients). During a follow-up of 3 years the incidence of severely symptomatic patients was 19% (79 of 420 patients) (Fig. 1).

Predictability of postoperative clinical outcome: The most important pre- and perioperative clinical and angiographic variables are presented in Tables I, II and III. Multivariate analysis showed that 3 variables had independent predictive value for postoperative severe angina: a low preoperative coronary score, performance of endarterectomy, and absence of previous MI. Together, these 3 variables correctly predicted 60% of the patients with adverse clinical outcome and 62% of the patients with no or mild symptoms.

Explanatory factors for severe symptoms after bypass surgery: The results of pre-, peri- and postoperative angiographic variables are shown in Table IV and Figure 2. An adverse clinical outcome is associated with a higher corrected coronary score, caused by a lower patency rate. There were no differences in preoperative extent of CAD, the number of nonbypassed stenoses, or progression of disease in the native coronary circulation.

Reoperability, management and clinical outcome: Reoperability was assessed in 70 patients; 46% of them were unable to undergo reoperation for technical reasons. The actual management and resulting clinical outcome are shown in Figure 3. Intensive pharmacologic treatment was offered to all patients who could not undergo reoperation.

Discussion

Many patients suffer from angina pectoris after CABG. During a follow-up study of 75 unselected patients, Campeau et al[4] found a recurrence rate of angina pectoris of 38% at 1 year after operation, 45% at 3 years and 63% at 7 years. In a follow-up study of 748 patients for 5 to 94 months, Cameron et al[5] found a recurrence rate of angina of 21% at 1 year to 37% at 6 years. The severity of angina was generally milder than before operation. The European Coronary Surgery Study[6] reported a postoperative recurrence rate of angina of 42% at 1 year and 51% at 3 years. In approximately half of the patients the symptoms were unchanged or even

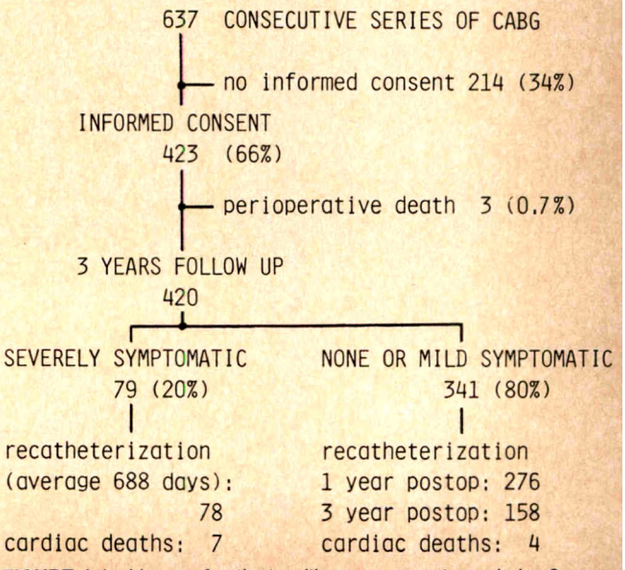

FIGURE 1. Incidence of patients with severe symptoms during 3 years follow-up after coronary artery bypass surgery (CABG).

TABLE I Predictive Value of Clinical Variables

Variable	Severely Symptomatic Patients (n = 79) n (%)	No or Mild Symptoms (n = 340) n (%)	p Value
Men	73 (92)	316 (93)	NS
Age >53 yr	35 (44)	171 (50)	NS
History of MI	46 (58)	240 (71)	NS
Cigarette smoker	77 (97)	295 (87)	NS
Cerebrovascular disease	21 (27)	80 (24)	NS
Diastolic BP >100 mm Hg	33 (42)	101 (30)	NS
Diabetes mellitus	6 (8)	17 (5)	NS
Family history of CAD	41 (52)	178 (52)	NS
4th heart sound	17 (22)	43 (13)	NS
CT ratio >0.5	40 (51)	167 (49)	NS
Total serum cholesterol >7.0 mmol/liter	35 (44)	146 (43)	NS
Serum triglycerides >2.5 mmol/liter	22 (28)	91 (27)	NS

p value: univariate analysis, χ^2 test.
BP = blood pressure; CAD = coronary artery disease; CT = cardiothoracic; MI = myocardial infarction; NS = not significant.

TABLE II Predictive Value of Preoperative Angiographic Variables

Variable	Severely Symptomatic Patients (n = 79) n (%)	No or Mild Symptoms (n = 340) n (%)	p Value
Pain during APST	36 (46)	158 (46)	NS
LVEDP >13 mm Hg	35 (44)	183 (54)	NS
EF >0.60	38 (48)	139 (41)	NS
3-vessel CAD	43 (54)	208 (61)	NS
Multivessel CAD	66 (84)	291 (86)	NS
Preoperative coronary score >15	23 (29)	138 (41)	<0.05

p value: univariate statistics, χ^2 test.
APST = atrial pacing stress test; CAD = coronary artery disease; EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; NS = not significant.

TABLE III Predictive Value of Perioperative Variables

Variable	Severely Symptomatic Patients (n = 79) n (%)	No or Mild Symptoms (n = 340) n (%)	p Value
Multiple grafts placed	69 (87)	280 (82)	NS
Lowest flow per graft <45 ml	49 (62)	211 (62)	NS
Total graft flow >50 ml	64 (81)	292 (86)	NS
Coronary endarterectomy	39 (49)	126 (37)	0.05
Duration ECC >110 min.	36 (46)	155 (46)	NS
Duration ACC >35 min.	37 (47)	138 (41)	NS
Perioperative infarction	4 (5)	18 (5)	NS
IABP assistance	3 (4)	24 (7)	NS

p value: univariate analysis, χ^2 test. ACC = aortic cross-clamping time; ECC = extracorporeal circulation; IABP = intraaortic balloon pumping; NS = not significant.

worse than before operation. Rahimtoola[7] reported that CABG reduced symptoms in 76 to 90% of patients; 33 to 55% became asymptomatic, 5 to 6% showed deterioration of symptoms after surgery, and angina recurred at an annual rate of 2 to 4%.

Laird-Meeter et al[8] studied 1,041 patients with a follow-up of 1 to 10 years (mean 3.5). The incidence of postoperative angina pectoris at 1 year was 30%, at 3 years 46% and at 8 years 50%. However, 89% of these symptomatic patients felt themselves improved by surgery. In this study, approximately 40% of the operated patients reported angina pectoris during a follow-up period of 3 years, which is in agreement with the studies cited earlier. Half of these patients had severe angina pectoris. Thus the incidence of severe symptomatic patients with NYHA class III to IV during a 3-year follow-up was 19%; most of the patients had class III symptoms.

Predictability of clinical outcome after bypass surgery: Obviously, patient management could be

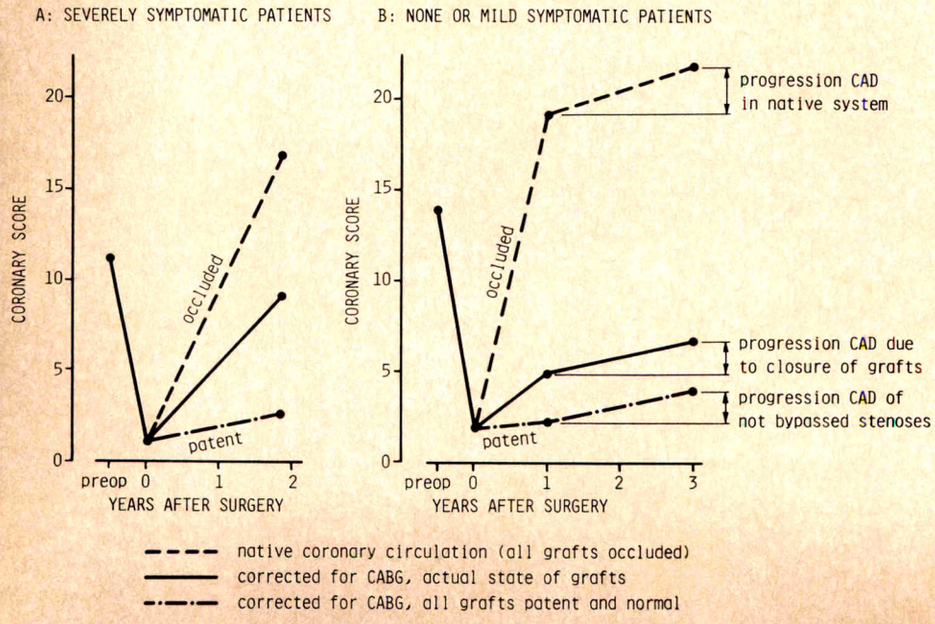

FIGURE 2. Progression of coronary artery disease (CAD) in severely symptomatic patients (**A**) and asymptomatic or mildly symptomatic patients (**B**). CABG = coronary artery bypass graft surgery.

TABLE IV Explanatory Factors for Severe Symptoms After Coronary Artery Bypass Grafting

Variable	Severely Symptomatic (n = 79)	No or Mild Symptoms (n = 340)	
	Preoperative		
LV end-diastolic pressure	17 ± 8	17 ± 6 (NS)	
Ejection fraction	0.59 ± 0.11	0.58 ± 0.11 (NS)	
Preoperative coronary score	11.3 ± 7.7	14.2 ± 7.2 ($p < 0.05$)	
Perioperative coronary score (all grafts assumed open)	1.1 ± 2.1	1.8 ± 3.0 (NS)	
No. of grafts placed	2.3 ± 0.8	2.3 ± 0.8 (NS)	
	Postoperative		
No. of recatheterizations	78	276	162
Follow-up after surgery (range, SD) (days)	688 days 20–1533, 425	1 year 271–776, 66	3 years 912–1462, 84
Postoperative coronary score			
Native coronary circulation	17 ± 9	19 ± 8 (NS)	22 ±9 ($p < 0.01$)
Corrected score (grafts in actual state)	9.2 ± 7.8	5.0 ± 5.7 ($p < 0.001$)	6.8 ± 7.5 ($p < 0.05$)
Corrected score (grafts assumed open)	2.7 ± 4.3	2.3 ± 3.6 (NS)	4.1 ± 4.9 (NS)
Patency rate grafts	55%	82% ($p < 0.0001$)	80% ($p < 0.0001$)

Values are mean + standard deviation.
p value: univariate statistics, unpaired *t* test, no symptoms vs symptoms.
NS = not significant; SD = standard deviation.

improved if adverse postoperative outcome could be predicted. Of the approximately 80 analyzed clinical, angiographic and perioperative variables, 3 variables were associated with clinical outcome, but classified outcome correctly in only 61% of all patients. This predictive value is too low to be clinically useful.

Explanatory factors for severe symptoms after bypass surgery: Postoperative angina pectoris is often related to incomplete revascularization, early closure of grafts or progression of coronary sclerosis in the native coronary arteries.[4,9–13] Adverse clinical outcome was associated with a higher attrition rate of grafts, whereas no differences were found in the rate of incomplete revascularization or progession of CAD in the native system of patients with no or mild symptoms compared with those who had severe symptoms. We do not know the reason for this higher graft closure rate in the symptomatic patients; although a low intraoperative graft flow, performance of endarterectomy and perioperative complications are associated with a higher graft attrition rate,[14] these findings do not imply that all these patients became severely symptomatic, as was the endpoint in this study.

Reoperability rate, management and clinical outcome of severely symptomatic patients: The reoperability rate of severely symptomatic patients was about 50%. In the remainder, coronary anatomy was unsuitable for further surgery. With intensive medical treatment, 50% of these patients improved to NYHA class I or II. Most of the reoperable patients were initially offered intense medical treatment before repeat surgery was advised; with such treatment about one-third of the patients improved to class I or II symptoms. The others underwent reoperation, after which 83% improved to class I, II or III.

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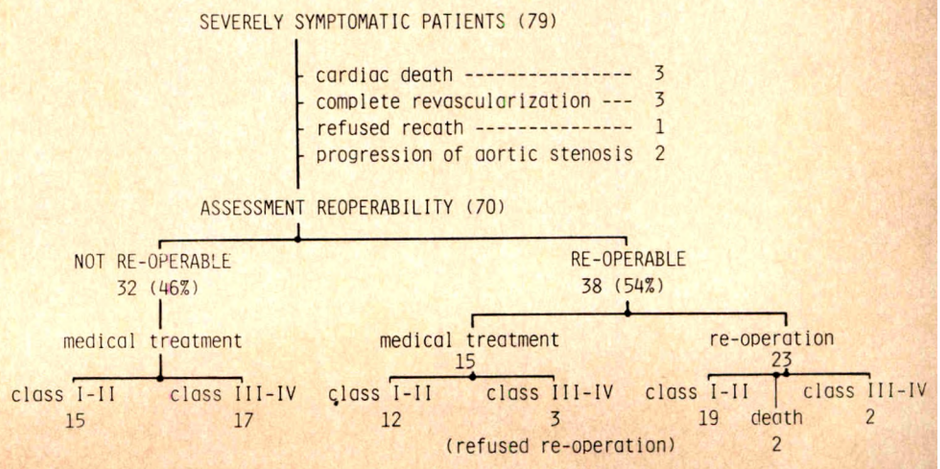

FIGURE 3. Reoperability rate, management and clinical course of patients with severe symptoms after bypass surgery.

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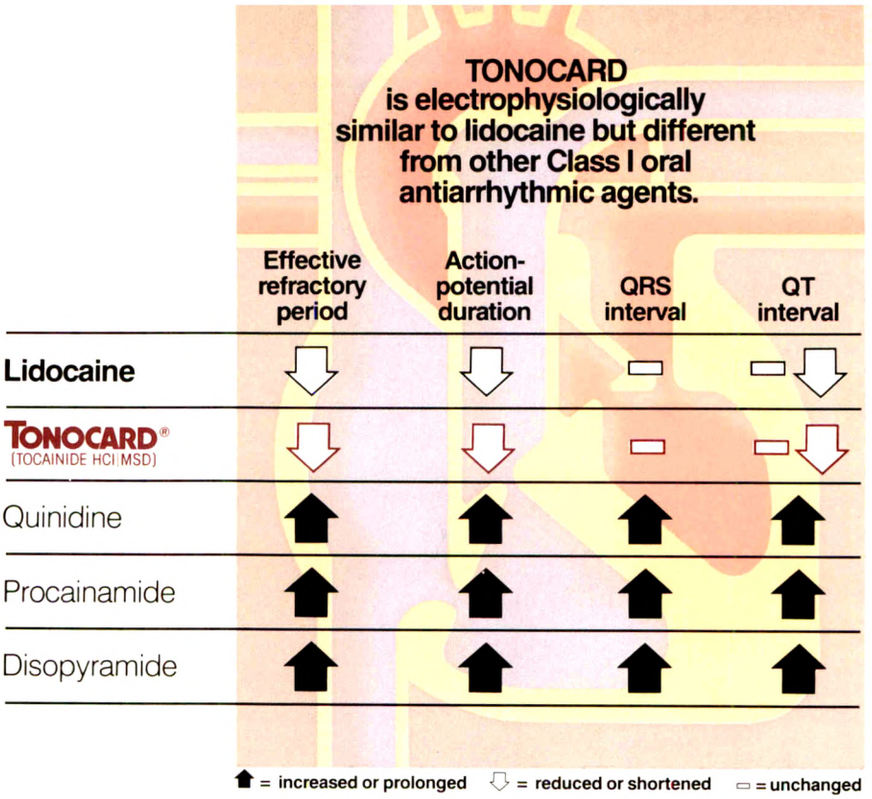

Adapted from Braunwald, E.: Pharmacologic treatment of cardiovascular disorders, in *Harrison's Principles of Internal Medicine*, ed. K. J. Isselbacher et al., 9th ed., New York, McGraw-Hill Book Company, 1980, pp. 1068-1069. Data derived from animal and human studies.

☐ Patients who respond to lidocaine also respond to TONOCARD in a majority of cases. Failure to respond to lidocaine usually predicts failure to respond to TONOCARD, but there are exceptions.

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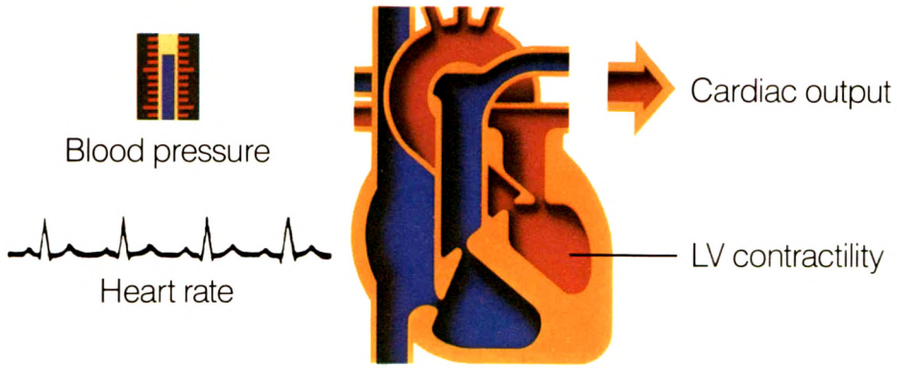
Clinical cardiac parameters were usually unchanged in well-compensated patients studied.

- In a long-term study of 72 post-myocardial infarction patients, TONOCARD (400 mg q 8 h) did not produce clinically significant changes in blood pressure, heart rate, or LV contractility.



- In catheterization studies, TONOCARD usually produced a small degree of depression in left ventricular function, but there were usually no changes in cardiac output or clinical evidence of increasing congestive heart failure.

TONOCARD has been used safely in patients with acute myocardial infarction and various degrees of congestive heart failure. It has, however, a small negative inotropic effect and can increase peripheral resistance slightly.

- TONOCARD should be used cautiously in patients with known heart failure or minimal cardiac reserve, particularly if a beta blocker is given as well, because of the potential for aggravating the degree of heart failure.

TONOCARD is contraindicated in patients who are hypersensitive to this product or to local anesthetics of the amide type and in patients with second- or third-degree atrioventricular block in the absence of an artificial ventricular pacemaker.

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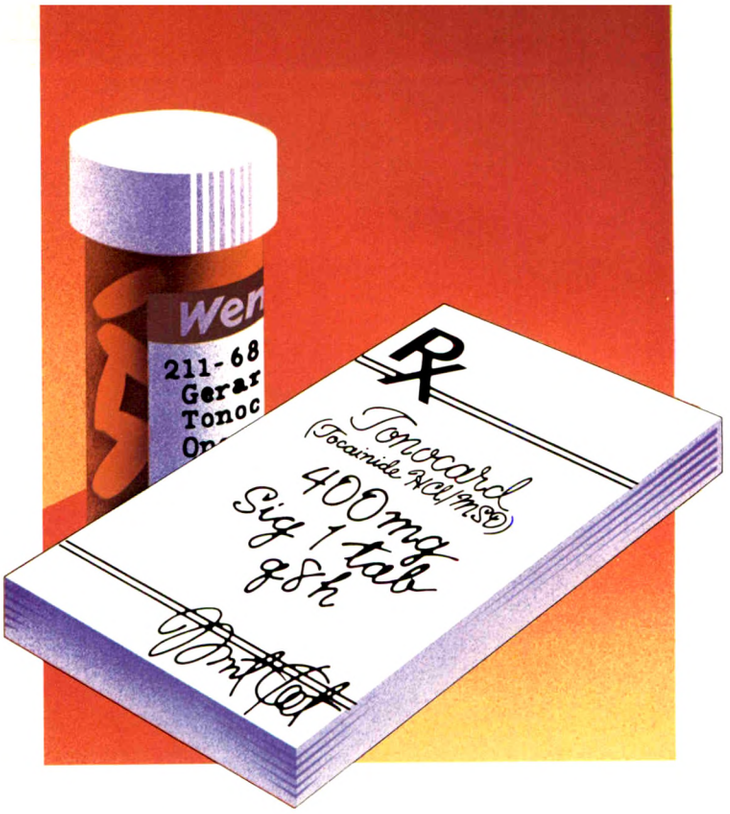

☐ Simple initial q 8 h dosage.

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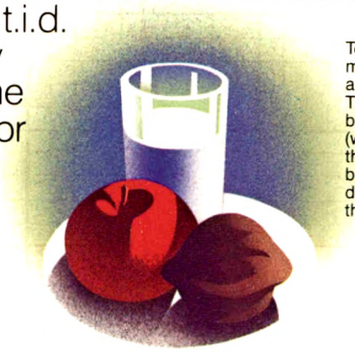
Recommended initial dosage is 400 mg every 8 hours; patients should then be carefully titrated on the basis of antiarrhythmic response and tolerance, both of which are dose-related. The usual adult dosage is between 1200 and 1800 mg/day, divided in three doses. Doses beyond 2400 mg have been administered infrequently. Patients who tolerate the t.i.d. regimen may be tried on a twice-daily regimen with careful monitoring. Some patients, particularly those with renal or hepatic impairment, may be treated with less than 1200 mg/day.



To help alleviate the most common adverse reactions, TONOCARD may be given with food (without affecting the extent of its bioavailability), the dosage reduced, or therapy discontinued.

Like other antiarrhythmics, tocainide has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like other antiarrhythmics, it has potentially serious adverse effects including the ability to worsen arrhythmias. It is therefore essential that each patient given tocainide be evaluated electrocardiographically and clinically prior to and during tocainide therapy to determine whether the response to tocainide supports continued treatment.

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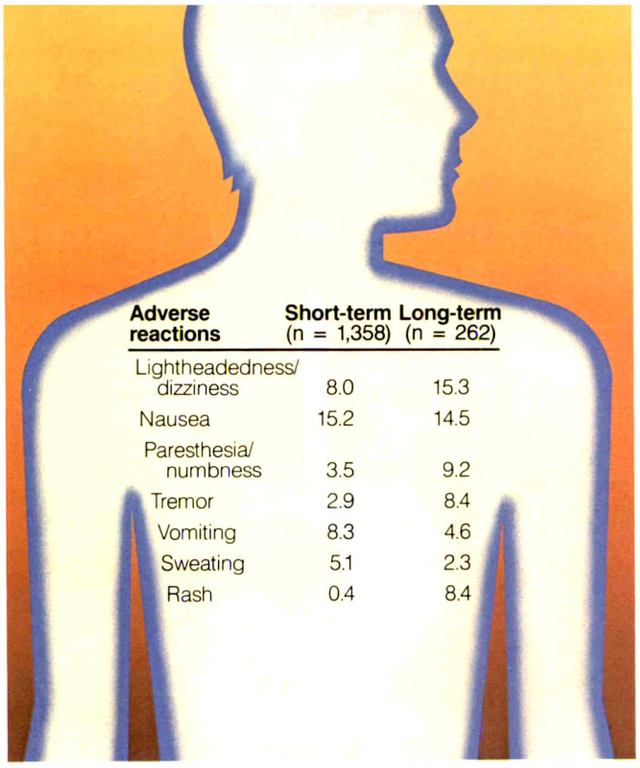


Reactions leading to therapy discontinuation occurred in 21% of patients in long-term (2 to 6 months) controlled trials.

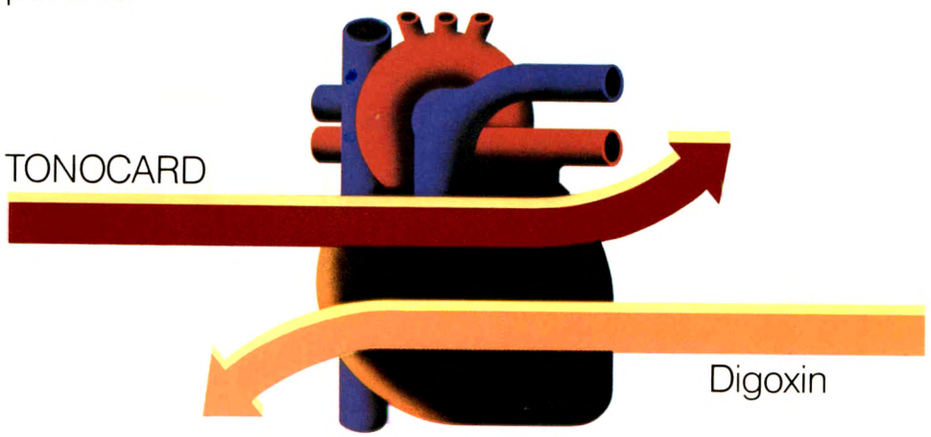
The most frequently reported adverse reactions, expressed as a percentage of patients receiving TONOCARD® (Tocainide HCl, MSD) in short-term and long-term controlled clinical trials.

- ☐ These adverse reactions were generally mild, transient, dose-related, and reversible with reduction in dosage, by taking the drug with food, or by therapy discontinuation.
- ☐ Tremor may be useful as a clinical indicator that the maximum dose is being approached.

CNS and GI reactions are common...

No interaction seen with digoxin.

- ☐ In specific interaction studies and open clinical studies with digoxin and TONOCARD, no clinically significant interaction was seen.
- ☐ TONOCARD is equally effective in digitalized and nondigitalized patients.



Other antiarrhythmics, anticoagulants, and diuretics were given with TONOCARD in open studies, without evidence of clinically significant interaction.

Beta blockers have been used with TONOCARD in open studies, without evidence of clinically significant interaction.

- ☐ However, in a specific interaction study, TONOCARD and metoprolol had additive effects on wedge pressure and cardiac index.

Caution should be exercised in the use of multiple-drug therapy.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing excessive depression of cardiac conductivity.

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Like other antiarrhythmics, tocainide has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given tocainide be evaluated electrocardiographically and clinically prior to, and during, tocainide therapy to determine whether the response to tocainide supports continued treatment.

CONTRAINDICATIONS: Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second or third degree atrioventricular block in the absence of an artificial ventricular pacemaker.

WARNINGS: ***Blood Dyscrasias:*** Leukopenia, agranulocytosis, hypoplastic anemia, and thrombocytopenia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill and who were receiving concomitant drugs. Patients should be instructed to promptly report the development of bruising or bleeding and any signs of infection such as fever, sore throat, or chills. Periodic blood counts are recommended, particularly during the first six months of therapy. If any of these hematologic disorders is identified, TONOCARD should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within one month of discontinuation (see ADVERSE REACTIONS).

Acceleration of Ventricular Rate. Acceleration of ventricular rate occurs infrequently when antiarrhythmics are administered to patients with atrial flutter or fibrillation (see ADVERSE REACTIONS).

PRECAUTIONS: *General* ***Pulmonary Fibrosis:*** Pulmonary fibrosis, pneumonitis, alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, TONOCARD should be discontinued (see ADVERSE REACTIONS).

In patients with known heart failure or minimal cardiac reserve, TONOCARD should be used with caution because of the potential for aggravating the degree of heart failure.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing depression of cardiac conductivity.

In patients with severe liver or kidney disease, the rate of drug elimination may be significantly decreased (see DOSAGE AND ADMINISTRATION).

Since antiarrhythmic drugs may be ineffective in patients with hypokalemia, the possibility of a potassium deficit should be explored and, if present, the deficit should be corrected.

Like all other oral antiarrhythmics, TONOCARD has been reported to increase arrhythmias in some patients (see ADVERSE REACTIONS).

Drug Interactions: Specific interaction studies with digoxin and metoprolol have been conducted; no clinically significant interaction was seen with digoxin, but tocainide and metoprolol had additive effects on wedge pressure and cardiac index. TONOCARD has also been used in open studies with digitalis, beta-blocking agents, other antiarrhythmic agents, anticoagulants, and diuretics, without evidence of clinically significant interactions. Nevertheless, caution should be exercised in the use of multiple drug therapy.

TONOCARD is equally effective in digitalized and nondigitalized patients. In 17 patients with refractory ventricular arrhythmias on concomitant therapy, serum digoxin levels (1.1 ± 0.4 ng/mL) remained in the expected normal range (0.5-2.5 ng/mL) during tocainide administration.

Pregnancy: Pregnancy Category C. In a teratogenicity study in rabbits, tocainide was administered orally at doses of 25, 50, and 100 mg/kg/day (about 1 to 4 times the usual human dose). No evidence of a drug-related teratogenic effect was noted; however, these doses were maternotoxic and produced a dose-related increase in abortions and stillbirths. In a teratogenicity study in rats, an oral dose of 300 mg/kg/day (about 12 times the usual human dose) showed no evidence of treatment-related fetal malformations, but maternotoxicity and an increase in fetal resorptions were noted. An oral dose of 30 mg/kg/day (about twice the usual human dose) did not produce any adverse effects.

In reproduction studies in rats at maternotoxic oral doses of 200 and 300 mg/kg/day (about 8 and 12 times the usual human dose, respectively), dystocia, and delayed parturition occurred which was accompanied by an increase in stillbirths and decreased survival in offspring during the first week postpartum. Growth and viability of surviving offspring were not affected for the remainder of the lactation period.

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There are no adequate and well-controlled studies in pregnant women. TONOCARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether tocainide is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from TONOCARD, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: TONOCARD commonly produces minor, transient, nervous system and gastrointestinal adverse reactions, but is otherwise generally well tolerated. TONOCARD has been evaluated in both short-term (n = 1,358) and long-term (n = 262) controlled studies as well as a compassionate use program. Dosages were lower in most of the controlled studies (1200 mg/day) and higher in the compassionate use program (1800 mg and more). In long-term (2-6 months) controlled studies, the most frequent adverse reactions were lightheadedness/dizziness (15.3 percent), nausea (14.5 percent), paresthesia/numbness (9.2 percent), and tremor (8.4 percent). These reactions were generally mild, transient, dose-related and reversible with a reduction in dosage, by taking the drug with food, or by therapy discontinuation. Tremor, when present, may be useful as a clinical indicator that the maximum dose is being approached. Adverse reactions leading to therapy discontinuation occurred in 21 percent of patients in long-term controlled trials and were usually related to the nervous system or gastrointestinal system.

Adverse reactions occurring in greater than one percent of patients from the short-term and long-term controlled studies appear in the following table:

	Percent of Patients Controlled Studies	
	Short-term (n = 1,358)	Long-term (n = 262)
NERVOUS SYSTEM		
Lightheadedness/dizziness/ vertigo/giddiness	8.0	15.3
Paresthesia/numbness	3.5	9.2
Tremor/quivering/tremulousness	2.9	8.4
Confusion/disorientation/ hallucinations	2.1	2.7
Altered mood/awareness	1.5	3.4
Restlessness/shakiness/ nervousness	1.5	0.4
Blurred vision/visual disturbances	1.3	1.5
Discoordination/unsteadiness/ walking disturbances	1.2	0.0
Anxiety	1.1	1.5
Tinnitus/hearing loss	0.4	1.5
Ataxia	0.2	3.0
Nystagmus	0.0	1.1
GASTROINTESTINAL SYSTEM		
Nausea	15.2	14.5
Vomiting	8.3	4.6
Anorexia	1.2	1.9
Diarrhea/loose stools	0.0	3.8
CARDIOVASCULAR SYSTEM		
Hypotension	3.4	2.7
Bradycardia	1.8	0.4
Palpitations	1.8	0.4
Chest pain	1.6	0.4
Conduction disturbances	1.5	0.0
Left ventricular failure	1.4	0.0
OTHER		
Sweating/cold sweat/night sweats/ clammy	5.1	2.3
Headache	2.1	4.6
Tiredness/drowsiness/fatigue/ lethargy/lassitude/sleepiness	1.6	0.8
Hot/cold feelings	0.5	1.5
Rash/skin lesion	0.4	8.4

An additional group of about 2,000 patients has been treated in a program allowing for the use of TONOCARD under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy, and comparatively high doses of TONOCARD were used. Fifty-four percent of the patients continued in the program for one year or longer, and 12 percent were treated for longer than three years, with the longest duration of therapy being nine years. Adverse reactions leading to therapy discontinuation occurred in 12 percent of patients (usually central nervous system effects or rash). A tabulation of adverse reactions occurring in one percent or more of patients follows:

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	Percent of Compassio (n = 1,5
NERVOUS SYSTEM	
Lightheadedness/dizziness/ vertigo/giddiness	25.
Tremor/quivering/tremulousness	21.
Restlessness/shakiness/ nervousness	11.
Confusion/disorientation/ hallucinations	11
Altered mood/awareness	11
Ataxia	10
Blurred vision/visual disturbances	10
Paresthesia/numbness	9
Nystagmus	1
GASTROINTESTINAL SYSTEM	
Nausea	24
Anorexia	11
Vomiting	9
Diarrhea/loose stools	6
CARDIOVASCULAR SYSTEM	
Increased ventricular arrhythmias/ PVCs	10
CHF/progression of CHF	4
Tachycardia	3
Hypotension	1
Conduction disturbances	1
Bradycardia	1
OTHER	
Rash/skin lesion	12
Sweating/cold sweat/night sweats/ clammy	8
Arthritis/arthralgia	4
Myalgia	1
Lupus	1

Adverse reactions occurring in less than one per tients in either the controlled studies or the comp use program are as follows:

Nervous System: Coma, convulsions/seizure sion, psychosis, mental change, agitation, altered difficulty concentrating, diplopia, dysarthria, impa ory, increased stuttering/slurred speech, insomni disturbance, local anesthesia, nightmares, thirst, myasthenia gravis.

Gastrointestinal System: Abdominal pain/c constipation, dysphagia, gastrointestinal symptoi ing dyspepsia).

Cardiovascular System: Ventricular fibrillation, of acute myocardial infarction, cardiogenic shock, block, hypertension, increased QRS duration, pl carditis, prolonged QT interval, right bundle bra syncope, vaso-vagal episodes, cardiomegaly, sinu

Pulmonary System: Respiratory arrest, pulmon pulmonary embolism, pulmonary fibrosis, alvec monia, pneumonitis, dyspnea.

Other: Hematologic disorder (agranulocyt plastic anemia, anemia, leukopenia, thrombocyt creased ANA, urinary retention, polyuria/increase alopecia, cinchonism, claudication, cold extrer mouth, earache, edema, fever, hiccups, itching, l malaise, metallic/menthol taste, muscle twitching/sp pain, pain radiating from neck, pallor/flushed face on shoulder, yawning.

Leukopenia, agranulocytosis, hypoplastic ar thrombocytopenia, possibly drug related, hav ported (0.10 percent) in patients receiving TON controlled trials and the compassionate use progr hematologic disorders usually occurred after 2-1 therapy and two patients died. These events usuall in seriously ill patients who were receiving concom known to be associated with hematologic disc WARNINGS).

Pulmonary fibrosis, pneumonitis, alveolitis, edema, and pneumonia, possibly drug related, reported in patients receiving TONOCARD. The of pulmonary fibrosis was 0.03 percent in conti and the compassionate use program. These eve occurred in seriously ill patients. Symptoms of th nary disorders and/or x-ray changes usually occu ing 3-18 weeks of therapy and two patients PRECAUTIONS).

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Usefulness of Electrophysiologic Testing in Evaluation of Amiodarone Therapy for Sustained Ventricular Tachyarrhythmias Associated with Coronary Heart Disease

LEONARD N. HOROWITZ, MD, ALLAN M. GREENSPAN, MD, SCOTT R. SPIELMAN, MD, CHARLES R. WEBB, MD, JOEL MORGANROTH, MD, HESCHI ROTMENSCH, MD, NEIL M. SOKOLOFF, MD, ALAN P. RAE, MD, BERNARD L. SEGAL, MD, and HAROLD R. KAY, MD

The prognostic importance of electrophysiologic studies in patients with sustained ventricular tachyarrhythmias treated with amiodarone was prospectively studied in 100 consecutive patients. Sustained ventricular tachycardia (VT)/ventricular fibrillation (VF) was inducible in all patients before amiodarone therapy. After amiodarone administration 2 groups of patients were identified. In group 1 patients the ventricular tachyarrhythmia was no longer inducible and in group 2 patients the arrhythmia remained inducible. In group 1, no recurrent arrhythmia occurred during a follow-up of 18 ± 10 months. In group 2, 38 of 80 patients (48%) had arrhythmia recurrence during a follow-up of 12 ± 9 months. The difference between group 1 and 2 could not be explained by clinical variables, amiodarone doses or plasma concentrations, or electrocardiographic variables. In patients in whom cardiovascular collapse or other severe symptoms where noted during electrophysiologic study after amiodarone treatment, recurrences caused sudden death (n = 12). However, in patients in whom the induced arrhythmia produced moderate symptoms, the recurrent arrhythmia was nonfatal VT (n = 26). Electrophysiologic testing provides clinical guidance and predicts prognosis in patients treated with amiodarone as it does for the evaluation of other antiarrhythmic agents.

(Am J Cardiol 1985;55:367–371)

The value of clinical electrophysiologic testing in the evaluation of amiodarone for the treatment of ventricular tachyarrhythmias has been controversial. It has been suggested that, unlike most other antiarrhythmic agents that have been extensively evaluated, the continued inducibility of a ventricular tachyarrhythmia during amiodarone therapy does not accurately predict subsequent clinical recurrences of arrhythmia. Therefore, some investigators recommend that amiodarone be used empirically in patients with even life-threatening ventricular tachyarrhythmias.[1–3] The present study was designed to prospectively assess the clinical value of electrophysiologic testing in patients with ventricular tachycardia (VT) ventricular fibrillation (VF), or both, treated with amiodarone.

From the Division of Clinical Cardiac Electrophysiology and the Computer Center of the Likoff Cardiovascular Institute, Hahnemann University Hospital and School of Medicine, Philadelphia, Pennsylvania. Manuscript received August 16, 1984; revised manuscript received October 4, 1984, accepted October 5, 1984.

Address for reprints: Leonard N. Horowitz, MD, Likoff Cardiovascular Institute, Hahnemann University and Hospital, Broad and Vine Street, Philadelphia, Pennsylvania 19102.

Methods

One hundred consecutive patients who had symptomatic sustained ventricular tachyarrhythmias complicating coronary artery disease (CAD) and who were treated with amiodarone were studied prospectively. To avoid biases that could confound analysis of the results, no patient's clinical management was altered by the results of the electrophysiologic evaluation and no additional antiarrhythmic interventions (pharmacologic or surgical) were undertaken in any patient until an arrhythmia recurred. By study design all patients who were started on amiodarone therapy continued unless side effects or arrhythmia recurrence caused an alteration or discontinuation of therapy. There were 86 men and 14 women, aged 38 to 78 years (mean 61). All patients had CAD, 97 of whom had had a myocardial infarction. The indication for electrophysiologic study was recurrent VT in 67 patients and cardiac arrest in 33. The left ventricular ejection fraction,

measured by radionuclide angiography, ranged from 8 to 52% (mean 25%).

In no patient was the spontaneous ventricular arrhythmia related to acute ischemia, metabolic or electrolyte abnormalities, or the proarrhythmic effects of drugs. Because this study was designed to evaluate the usefulness of electrophysiologic testing in the evaluation of amiodarone, only patients in whom sustained VT or VF was inducible in the baseline state were included in this study.

Before amiodarone treatment: All patients underwent an initial electrophysiologic study after all antiarrhythmic drugs had been discontinued for at least 5 half-lives. Their elimination was documented by plasma concentration measurement. Patients then underwent serial drug studies to evaluate the efficacy of standard and investigational agents in preventing initiation of VT or VF. The number of studies before amiodarone ranged from 0 to 7 (mean 2.6). Antiarrhythmic regimens tested before amiodarone included procainamide (76 patients), quinidine (55 patients), disopyramide (3 patients), mexiletine (48 patients), phenytoin (3 patients), the combination of procainamide or quinidine with mexiletine (51 patients), flecainide (6 patients), indecainide (7 patients) and bethanidine (2 patients). If no released or investigational agent or combination regimen prevented initiation of the arrhythmia or if the patient did not tolerate a regimen that did prevent initiation of ventricular tachyarrhythmia, amiodarone was selected for therapy.

Amiodarone administration: Amiodarone therapy was initiated with either an oral or an oral plus intravenous regimen. In the oral protocol, patients received 1,000 mg/day on days 1 through 7 and 800 mg/day on days 8 through 14. Electrophysiologic testing was performed on day 13, 14 or 15. In the oral-plus-intravenous protocol, patients received 10 mg/kg/24 hours of amiodarone by continuous intravenous infusion and 600 mg/day orally on days 1 through 3. The intravenous infusion was discontinued and the patients received 800 mg/day orally on days 4 through 10. Electrophysiologic testing was performed on day 9, 10 or 11 in this protocol.

In all cases, electrophysiologic testing was performed while the patient was receiving amiodarone as the only antiarrhythmic agent. If a hemodynamically significant, symptomatic ventricular tachyarrhythmia remained inducible, procainamide or quinidine was added and electrophysiologic testing was repeated unless contraindicated by clinical history or other factors. A beneficial response to the combination regimen was either inability to initiate the arrhythmia, or if the VT remained inducible, it was slower and less symptomatic.

Electrophysiologic protocol and definitions: The same stimulation protocol was used in every study. This included the introduction of 1, 2 and 3 ventricular extrastimuli during sinus rhythm and ventricular pacing at cycle lengths of 600 and 450 ms. The stimulus was a rectangular impulse (1 ms in duration) delivered at twice diastolic threshold. Stimulation was performed at the right ventricular apex in all patients, and if no arrhythmia was induced, then at the right ventricular outflow tract. Left ventricular stimulation was performed only in the initial study if an arrhythmia was not inducible with with right ventricular stimulation (3 patients). Left ventricular stimulation at 2 sites was repeated at the amiodarone study only when left ventricular stimulation was required during the initial study. The stimulation protocol was terminated only at the initiation of sustained VT or VF. If nonsustained VT was initiated, stimulation was continued until initiation of a sustained VT or VF or completion of the stimulation protocol.

Responses to stimulation during the baseline study were categorized as: (1) Sustained VT, defined as a tachycardia which lasted more than 30 seconds or required termination within 30 seconds because of hemodynamically significant symptoms. (2) VF, defined as the induced rhythm when, within 3 seconds of the initiation of a sustained ventricular tachyarrhythmia, the surface electrocardiogram showed VF. If a tachyarrhythmia remained organized for more than 3 seconds it was termed VT even if it subsequently spontaneously degenerated to VF.

An arrhythmia was defined as *inducible* after amiodarone if VT or VF was initiated by any part of the complete stimulation protocol delivered to both the right ventricular apex and right ventricular outflow tract regardless of the mode of stimulation that initiated the tachyarrhythmia before amiodarone. An arrhythmia was considered *not inducible* after amiodarone if fewer than 16 complexes of VT were initiated using the complete stimulation protocol delivered to both the right ventricular apex and right ventricular outflow tract.[4]

Symptoms during the VT/VF induced at the postamiodarone study were classified as severe if the arrhythmia produced cardiovascular collapse, severe angina or near syncope. The symptoms were not severe if lightheadedness, palpitations or transient dizziness occurred.

Antiarrhythmic medications and follow-up: All patients were discharged on amiodarone, 600 mg/day. This dose was reduced to 400 mg after 4 months in all patients continuing to receive medication at that point. In 8 patients the dose was subsequently reduced to less than 400 mg because of the development of side effects. An additional antiarrhythmic drug was used in 13 patients based on the results of electrophysiologic testing. Patients were followed in a research arrhythmia clinic and were seen 1 month after discharge, every 4 months during the first year, and every 6 months thereafter. Holter monitor recordings were obtained at each clinic visit. Active attempts were made to obtain electrocardiographic documentation of any symptomatic episode compatible with recurrent arrhythmia using Holter monitoring, transtelephonic electrocardiographic transmissions and in-hospital telemetric monitoring.

Sudden death or electrocardiographically documented symptomatic VT occurring more than 1 month after starting amiodarone were classified as recurrent arrhythmia. Sudden cardiac death was defined as an unexpected, witnessed death occurring within 1 hour of the onset of symptoms and a catastrophic change in the state of health that could not be explained by obvious causes. If the death was not witnessed the patient must have been seen within the previous 12 hours and been free of chest pain. If a patient was resuscitated from an arrhythmic event, that event was considered a sudden cardiac death for statistical purposes. Nonarrhythmic cardiac death was caused by progressive congestive heart failure or myocardial infarction. Since there are many potential causes for syncope in this patient population, we did not consider the occurrence of syncope from which the patient recovered without resuscitation or bystander assistance and in whom no electrocardiographic documentation of recurrent VT was obtained, to be the result of recurrent VT.

The duration of follow-up was calculated from the date amiodarone was started to either the time of first arrhythmia recurrence (38 patients), death (9 patients), discontinuation of amiodarone because of side effects (9 patients) or September 1, 1984 (44 patients).

Statistical methods: Standard life-table analysis techniques[5] were used to summarize results. The response variable was recurrence of the arrhythmia. Patients in whom amiodarone side effects caused drug discontinuation were considered censored as of the date of discontinuation. Patients who died without documented recurrence (i.e., patients who died from nonarrhythmic causes) were considered censored

as of the date of death. Patients who died suddenly were considered to have had a recurrence as of the date of death. No patient was lost to follow-up. The Mantel-Cox and Breslow statistics were used to test the equality of survival curves.

Contingency table analyses were calculated using either chi-square or Fisher's exact tests. A Student t test and analysis of variance techniques were used to test for intergroup differences. A p value <0.05 was considered significant.

Results

All 100 patients in this study had sustained VT or VF inducible at the initial electrophysiologic study. Monomorphic VT was inducible in 95 patients and VF was inducible in 5 patients. After amiodarone loading, 2 groups of patients were identified by electrophysiologic testing: In group 1 patients, the tachyarrhythmia was no longer inducible and in group 2 patients, it remained inducible.

Group 1 consisted of 20 patients. The induced arrhythmias before amiodarone treatment in this group included VT in 18 patients and VF in 2 patients. In 18 patients, noninducibility was achieved with amiodarone alone and in 2 patients the combination of amiodarone and procainamide produced a noninducible response. All patients were treated with the regimen that produced a noninducible response. Follow-up in group 1 ranged from 4 to 31 months (mean 18). Except for 1 patient, who died of myocardial infarction 4 months after starting amiodarone therapy, the minimum follow-up in this group was 12 months. There were no recurrent symptomatic VT or VF and no sudden deaths in this group. Two patients died of nonarrhythmic cardiac causes. Amiodarone was discontinued because of side effects in 3 patients.

Group 2 consisted of 80 patients. The amiodarone induced arrhythmias before amiodarone treatment were VT (77 patients) and VF (3 patients). After amiodarone treatment, sustained VT was induced in 76 patients, VF in 2 patients and nonsustained VT in 2 patients. Amiodarone alone was used in 69 patients, and 11 patients were treated with amiodarone in combination with either procainamide (7 patients) or quinidine (4 patients). Follow-up in group 2 ranged from 2 to 32 months (mean 12). Symptomatic VT or VF recurred in 38 of 80 patients (48%). Seven patients died from nonarrhythmic cardiac causes in group 2. Amiodarone was discontinued because of toxicity in 6 patients.

The recurrent VT or VF occurred between 1 and 3 months after hospital discharge in 20 patients and between 3 and 18 months after discharge in 18 patients. The dose of amiodarone at the time of recurrence was 600 mg/day in 21 patients, 400 mg/day in 14 and less than 400 mg/day in 3.

The difference in recurrence-free interval between groups 1 and 2 was highly significant using either the Breslow and Mantel-Cox analyses (Fig. 1). Groups 1 and 2 were not significantly different with respect to baseline ventricular tachyarrhythmia, ejection fraction (25 vs 24%), age or severity of heart disease.

The amiodarone doses and plasma concentrations were analyzed using 2-way analysis of variance techniques to ascertain whether differences in these parameters could explain the difference between groups 1 and 2. There were no differences between group 1 and 2 in amiodarone plasma concentrations at the time of electrophysiologic study or during follow-up (Table I). Similarly, there was no significant difference during follow-up in amiodarone dose (391 [range 243 to 400] vs 432 [range 300 to 600] mg/day) or QTc interval (462 [range 350 to 520] vs 471 [range 380 to 580] ms) between groups 1 and 2.

TABLE I Comparison of Mean Amiodarone Plasma Levels (mg/liter) by Group and Time of Measurement

	Group I Noninducible (n = 11)	Group II Inducible (n = 69)
Time of measurement electrophysiologic study	1.41	1.71
Follow-up level*	1.77	2.06
Analysis of Variance Table		
Effect on amiodarone level	F	p
Group (I or II)	2.23	0.14
Time of measurement	3.19	0.08
Interation	0.00	0.96

* Follow-up level is either the last measured amiodarone plasma level before recurrence or the most recently measured amiodarone plasma level in patients without recurrence.

Two subgroups of patients (those with and those without recurrence) whose VT/VF remained inducible were analyzed in a similar fashion. There was no significant difference in amiodarone plasma concentrations between the subgroups (2.2 [range 0.7 to 3.8] vs 1.9 [range 0.5 to 3.5] mg/liter). Amiodarone dose in the recurrence-free subgroup was significantly lower than in the group with recurrent VT/VF (391 ± 91 vs 499 ± 110 mg/day, p <0.0001). The QTc interval in the 2 subgroups was not different (475 [recurrence] vs 457 [no

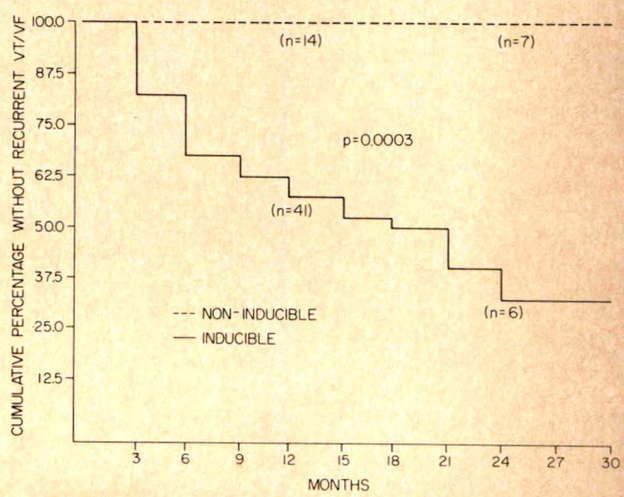

FIGURE 1. Life-table analysis of results in patients with and without inducible ventricular tachycardia/ventricular fibrillation (VT/VF) during amiodarone therapy. By 18 months, approximately 50% of patients with inducible VT/VF had a recurrence. The numbers in parentheses indicate the number of patients who remained available for analysis.

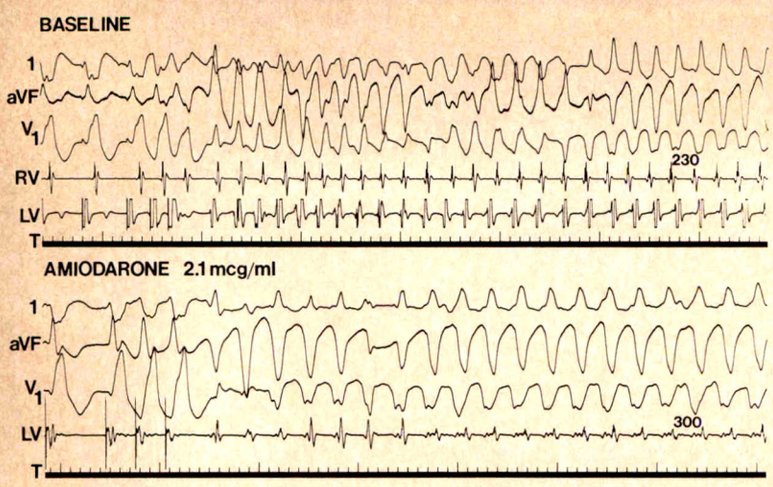

FIGURE 2. Electrophysiologic study in a patient who subsequently died suddenly. Electrocardiographic leads 1, aVF and V_1 are shown with right ventricular apical (RV) and left ventricular lateral wall (LV) intracardiac electrograms and 100-ms time marks (T). The pretreatment (BASELINE) study is shown in the **top** panel. Programmed stimulation initiated a uniform-morphology ventricular tachycardia (VT) (cycle length 230 ms) that produced syncope. Cardioversion was required for termination. After amiodarone loading, programmed stimulation initiated a slower VT (cycle length 300 ms) of similar morphology. This VT also produced syncope and cardioversion was required. This patient died suddenly 5 months after initiation of amiodarone therapy.

recurrence] ms). Other factors including baseline QTc, change in QTc, baseline and change in ventricular effective refractory period, and baseline and change in VT cycle length were analyzed and were not different between the subgroups.

Analysis of the arrhythmia recurrences within group 2 provided further evidence for the utility of electrophysiologic testing of amiodarone therapy. Of the 80 patients in whom the arrhythmia was inducible, 24 had severe symptoms (such as cardiovascular collapse) during their induced VT/VF after amiodarone loading; 12 (50%) subsequently died suddenly (Fig. 2). In each the induced VT/VF was sustained. In 8 it required cardioversion; in 4 it produced severe angina and near syncope before termination by pacing.

Fifty-six patients had inducible VT that did not produce severe symptoms. Twenty-six patients (46%) had a recurrence and none were fatal. Sustained VT was the arrhythmia induced after amiodarone loading in all 26 patients (Fig. 3). The VT cycle lengths were significantly shorter in the patients with severe symptoms during induced VT (304 [range 250 to 320] vs 411 [range 300 to 580] ms, $p = 0.005$).

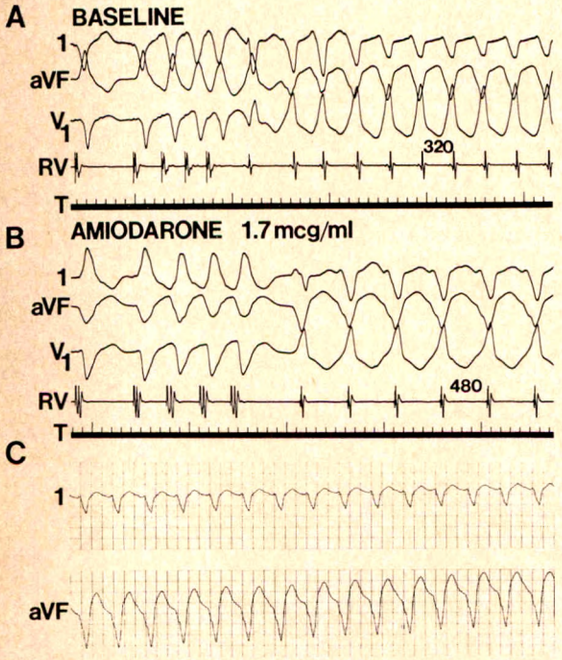

FIGURE 3. Electrophysiologic study and recurrent spontaneous ventricular tachycardia (VT) in a patient treated with amiodarone. **A** and **B,** electrocardiographic leads 1, aVF and V_1 with a right ventricular electrogram (RV) and 100-ms time marks (T). **C,** simultaneously recorded leads 1 and aVF are shown during spontaneous VT. **A,** during the pretreatment (BASELINE) study, VT (cycle length 320 ms) was induced with triple extrastimuli. **B,** after amiodarone loading, the VT was still inducible, although it was considerably slower (cycle length 480 ms). The VT induced during the posttreatment study produced palpations. **C,** electrocardiogram recorded during a spontaneous recurrence of VT during which the patient reported "mild rapid heart action."

Discussion

We have shown that electrophysiologic testing is useful in identifying patients at risk of recurrent VT/VF during amiodarone therapy. More important, those patients in whom adjunctive therapy with drugs, devices or surgery are indicated can also be identified.

The predictive value of electrophysiologic testing of antiarrhythmic regimens when applied to conventional antiarrhythmic drugs has been excellent.[4,6–8] The recurrence rates of VT/VF are high (> 75%) in patients treated with antiarrhythmic regimens which fail to prevent initiation of VT/VF during electrophysiologic testing. There is a consensus that this type of evaluation is effective and indicated in patients with life-threatening arrhythmias.[9,10] With regard to amiodarone, however, no such consensus exists.

Several early reports suggested that electrophysiologic testing might not be useful in the evaluation of amiodarone.[1–3,11,12] Hamer and et al[1] reported that although they induced VT in 8 of 9 patients during amiodarone treatment, no patient suffered recurrent VT. They suggested that the efficacy of amiodarone in patients with VT may not be reliably predicted by electrophysiologic studies. Subsequent studies by others appear to support this impression.[13–15] The conclusion of these reports was that the recurrence rate of VT/VF in patients treated with amiodarone was very low, and

although VT continued to be inducible, recurrence rates could not be attributed to this continued inducibility.

Other groups have reported conflicting results. McGovern and Ruskin[16] reported 30 patients in whom electrophysiologic studies were performed before and after amiodarone therapy was initiated. Of patients in whom VT was either no longer inducible or more difficult to initiate after amiodarone treatment, 16 patients were free of recurrent VT, whereas in 14 patients in whom amiodarone had no effect on arrhythmia inducibility, 8 (57%) had recurrent VT/VF within 28 months. Borggrefe et al[17] presented results similar to those of the present study in a group of 36 patients. In this study 8 of 23 patients (34%) whose arrhythmia remained inducible during amiodarone treatment had recurrent VT/VF, whereas none had recurrent arrhythmia when the arrhythmia was more difficult or impossible to induce during amiodarone treatment.

The difference in conclusions between these 2 groups of studies may be accounted for by several variables. Significant differences are apparent in study design, stimulation protocols, methods for assessing and adjusting therapy, loading and maintenance regimens and the duration of follow-up. These disparities may account for the differing conclusions.

The present study was performed prospectively with an unaltered protocol over the 3 years, during which patients were enrolled and data collected. No additional antiarrhythmic interventions were undertaken in any patient who had not had a recurrence of arrhythmia (an endpoint of the study). Finally, no patient's clinical management was altered by the results of this evaluation to avoid a bias toward following only "less ill" patients. The results of this study were not influenced by amiodarone dose or plasma concentration, and there were no apparent differences between patient groups with respect to the effects of amiodarone (such as QTc and change in VT cycle length). A regimen was used that was well tolerated by most patients and thus was clinically applicable for chronic antiarrhythmic therapy in a large population of patients with CAD and depressed left ventricular function.

Our data show a correlation between the results of electrophysiologic testing and subsequent clinical outcome in patients with life-threatening VT/VF treated with amiodarone. Furthermore, we have shown that such testing predicts the severity of recurrent ventricular tachyarrhythmias when they do occur. This information may be used prospectively to implement adjunctive antiarrhythmic therapy, such as antiarrhythmic devices or surgery in patients who were at risk of suffering sudden death.

For patients with inducible but slow and minimally symptomatic VT, a clinical trial of amiodarone is acceptable. However, in patients with a rapid VT on amiodarone, alternate forms of therapy should be explored because the almost 50% recurrence rate is unacceptably high for a life-threatening situation. We propose that electrophysiologic testing be used for the clinical management of patients with lethal arrhythmias treated with amiodarone. The contention that most patients treated with amiodarone for ventricular tachyarrhythmias will not have a recurrence is not supported by the data. An assessment of prognosis and the severity of the potential recurrence is critical for management. Amiodarone is an effective antiarrhythmic agent but it should be evaluated by electrophysiologic techniques, as are other agents, in patients with lethal ventricular arrhythmias.

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Cardiac Arrest and Sudden Death in Patients Treated with Amiodarone for Sustained Ventricular Tachycardia or Ventricular Fibrillation: Risk Stratification Based on Clinical Variables

LORENZO A. DICARLO, Jr., MD, FRED MORADY, MD, MARY JANE SAUVE, RN, MS, PATRICIA MALONE, RN, BS, JESSE C. DAVIS, MD, THOMAS EVANS-BELL, MD, STUART A. WINSTON, DO, and MELVIN M. SCHEINMAN, MD

Multivariate analysis of 11 clinical variables was performed in 104 patients with sustained, symptomatic ventricular tachycardia (VT) or ventricular fibrillation treated with amiodarone to determine variables predictive of subsequent cardiac arrest or sudden death. Twenty-five patients (24%) had fatal or nonfatal cardiac arrest after 7.3 ± 6.2 months (mean ± standard deviation) of therapy. Multivariate analysis identified an ejection fraction of less than 0.40, syncope or cardiac arrest before amiodarone therapy, and VT (3 or more consecutive ventricular premature complexes) during predischarge ambulatory electrocardiographic monitoring as variables associated with a high risk of subsequent fatal or nonfatal cardiac arrest ($p < 0.03$). Patients who had these 3 clinical variables had a much higher predicted incidence of cardiac arrest at 6 months (62%) and 12 months (76%) than did patients with an ejection fraction greater than 0.40, without syncope or cardiac arrest before amiodarone therapy, and without VT during predischarge ambulatory electrocardiographic monitoring (2% and 5%, respectively) ($p < 0.02$). Risk stratification using clinical variables can predict which patients are at high risk of recurrent cardiac arrest or sudden death during amiodarone therapy.

(Am J Cardiol 1985;55:372–374)

Patients who survive a cardiac arrest or who have recurrent, sustained ventricular tachycardia (VT) not controlled by conventional antiarrhythmic agents are at high risk of sudden death. Amiodarone has been reported to be effective in preventing recurrent VT or sudden death in 52 to 90% of these patients during mean follow-up periods of 8.6 to 21 months.[1–15] Clinical variables that predict which patients will benefit from long-term treatment with amiodarone are not known. Identification of patients who will have recurrent VT or ventricular fibrillation (VF) while being treated with amiodarone would allow selection of patients who might benefit from alternative forms of therapy, such as implantation of an automatic defibrillator, cardiac electrosurgery or use of other pharmacologic therapy. In this study, multiple clinical variables were analyzed in a group of 104 patients with recurrent VT or previous cardiac arrest to determine whether subgroups of patients at high risk of having recurrent VT or cardiac arrest during chronic amiodarone therapy could be identified.

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Address for reprints: Lorenzo A. DiCarlo, Jr., MD, Cardiac Electrophysiology Section, Division of Cardiology, Box 55, University Hospitals, 1405 East Ann Street, Ann Arbor, Michgan.

Methods

One hundred four consecutive patients with sustained, symptomatic VT or VF treated with amiodarone were included in this study. Sustained VT was defined as VT at least 30 seconds in duration or requiring direct-current cardioversion for termination. Before treatment with amiodarone, each patient had had 1 or more episodes of spontaneous VT or VF, and either a spontaneous recurrence of VT or VF despite therapy with 1 or more conventional antiarrhythmic agents (53 patients), or inducible VT during electropharmacologic testing with 1 or more conventional antiarrhythmic agents (51 patients). Patients with VT or VF occurring within the first 48 hours of an acute myocardial infarction were excluded. Patients with VT or VF due to electrolyte or metabolic

abnormalities, antiarrhythmic therapy or other remediable causes were also excluded.

All patients underwent 24 hours of continuous ambulatory electrocardiographic (ECG) monitoring before hospital discharge, after 6 to 10 days of amiodarone therapy. The ambulatory ECG cassette recordings were analyzed using a microprocessor-based, automated arrhythmia detection and analysis system (Instruments for Cardiac Research, Inc., model 6201). Ambulatory recordings were analyzed for frequency and morphologic pattern of ventricular premature complexes (VPCs). Thirty or more VPCs/hour were considered frequent, and fewer than 30 VPCs/hour were considered infrequent. Ventricular tachycardia was defined as 3 or more consecutive VPCs.

The patient's clinical characteristics are listed in Table I. Left ventricular ejection fraction was determined in 61 patients by contrast or radionuclide ventriculography and by 2-dimensional echocardiography in 26 patients.

Amiodarone therapy: Amiodarone was administered in oral doses of 800 to 1,600 mg/day for 5 to 14 days before hospital discharge. In patients with a history of frequent episodes of VT or cardiac arrest, intravenous amiodarone was administered as a continuous infusion of 1 g over 24 hours for 1 to 5 days before initiation of oral therapy. After discharge, amiodarone was continued for 2 months at a dose of 800 mg/day, followed by a maintenance dose of 600 mg/day. Further dose adjustments depended on the occurrence of adverse effects and clinical response. In patients with a history of cardiac arrest, a conventional type I agent (usually procainamide or quinidine) was added and discontinued after 6 to 8 weeks.

Follow-up: The minimal follow-up period in patients who did not have a recurrence of VT or VF was 6 months. Follow-up data were collected by personal interview or by telephone or mail contact with all patients and referring physicians. All recurrences of VT were documented by ambulatory ECG recordings or by ECG rhythm strips. A recurrence of VT was defined as symptomatic, sustained VT after at least 2 weeks of amiodarone therapy. Cardiac arrest was defined as loss of consciousness due to VT or VF requiring cardiopulmonary resuscitation and direct-current cardioversion or defibrillation. Sudden death was defined as unexpected death of natural causes occurring during sleep or within 1 hour of the patient's collapse. Amiodarone was discontinued because of an adverse drug reaction in 10 patients, and because of noncompliance in 3 others; these patients were included in the analysis up to the point of discontinuation of amiodarone therapy. Patients who died from nonarrhythmic causes were included in the analysis as survivors until the times of their deaths.

Statistical analysis: The following variables were evaluated: age, gender, presence of previous myocardial infarction, infarct location, presence of a ventricular aneurysm, aneurysm location, ejection fraction, New York Heart Association class, symptoms associated with VT or VF (palpitations, syncope, in-hospital cardiac arrest, out-of-hospital cardiac arrest), digitalis therapy, and the results of predischarge ambulatory ECG monitoring. Multivariate analysis was performed with the Cox regression.

TABLE I Clinical Characteristics of 104 Patients Treated with Amiodarone

Age (yr)	61 ± 13*
Males/females	81/23
Heart disease	
Coronary artery disease	82 (79%)
Remote MI (>6 weeks)	65 (79%)
Recent MI (≤6 weeks)	9 (11%)
Ventricular aneurysm	49 (60%)
Dilated cardiomyopathy	9 (8%)
Valvular heart disease	2 (2%)
None	11 (11%)
Symptoms before therapy	
Palpitations, CHF, lightheadedness	45 (44%)
Syncope	16 (15%)
In-hospital cardiac arrest	16 (15%)
Out-of-hospital cardiac arrest	27 (26%)
NYHA	
I–II	50 (48%)
III	54 (52%)
Ejection fraction	0.35 ± 0.15†

* Mean ± standard deviation.
† Determined in 87 patients (84%).
CHF = congestive heart failure; MI = myocardial infarction; NYHA = New York Heart Association functional class.

Results

Results of therapy: During a follow-up period of 15.7 ± 9.1 months (mean ± standard deviation), 63 patients (61%) had no recurrence of symptomatic, sustained VT, cardiac arrest or sudden death; their mean amiodarone dose was 442 ± 160 mg/day. Twenty-five patients (24%) had a cardiac arrest due to VT or VF, or sudden death, after 7.3 ± 6.2 months of amiodarone therapy (mean dose 567 ± 183 mg/day). Five patients in this group were successfully resuscitated. Sixteen of the 104 patients (15%) had a recurrence of symptomatic VT without cardiac arrest or sudden death after 8.7 ± 8.1 months of therapy with a mean dose of 513 ± 219 mg/day. There was no significant difference in the incidence of cardiac arrest or sudden death during the first 2 months of follow-up when patients who received adjunctive therapy with a type I antiarrhythmic agent were compared with those who did not.

Results of multivariate analysis: Three variables were identified as predictive of cardiac arrest during amiodarone therapy: ejection fraction less than 0.40 ($p < 0.03$), the occurrence of syncope or cardiac arrest before amiodarone therapy ($p < 0.01$), and the presence of VT on the predischarge ambulatory electrocardiogram ($p < 0.03$). The cumulative effect of these 3 variables on predicted survival is illustrated in Figure 1. Patients in the subgroup who had an ejection fraction of 0.40 or greater, no previous syncope or cardiac arrest, and no VT during predischarge ambulatory ECG monitoring were predicted to have a survival rate of 98% at 6 months and 95% at 18 months. Patients with an ejection fraction less than 0.40, previous syncope or cardiac arrest, and VT during predischarge ambulatory monitoring had a predicted survival of 38% at 6 months and 24% at 18 months. Intermediate survival rates were predicted for patients having any 1 or any 2 of the 3 variables predictive of poor outcome.

Discussion

The prognosis of patients treated with amiodarone after resuscitation from cardiac arrest has varied widely. Previous studies have reported survival rates of 85 to 97% during mean follow-up periods of 12 to 19 months.[9,10,14,16] Differences in length of follow-up and clinical characteristics of the patients in each study group may account for the different survival rates. The

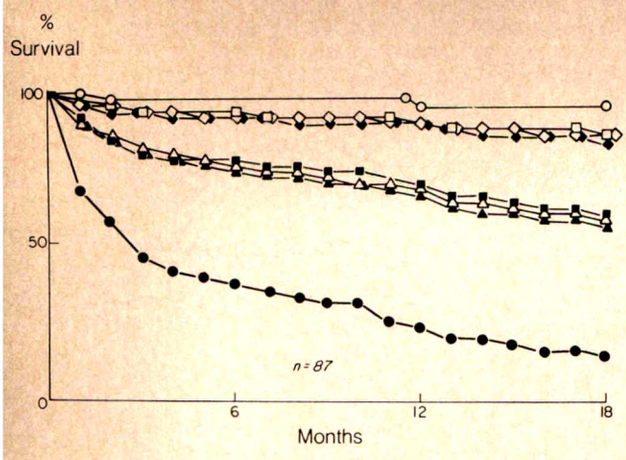

FIGURE 1. Cumulative effects of ejection fraction (EF), previous syncope or cardiac arrest (SYN/CA), and ventricular tachycardia (VT) during predischarge ambulatory electrocardiographic monitoring on predicted survival during amiodarone therapy EF ≥40, no SYN/CA, no VT (○); EF <40, no SYN/CA, no VT (□); EF ≥40, no SYN/CA, VT (◇); EF ≥40, SYN/CA, no VT (♦); EF <40, no SYN/CA, VT (■); EF <40, SYN/CA, no VT (△); EF ≥40, SYN/CA, VT (▲); EF <40, SYN/CA, VT (●). Statistical significance: EF, $p < 0.03$; SYN/CA, $p < 0.01$; VT $p < 0.03$.

results of our study suggest that patients treated with amiodarone can be stratified into subgroups at various degrees of risk for a poor clinical response. Multivariate analysis identified 3 variables associated with a high risk of cardiac arrest or sudden death: ejection fraction less than 0.40, syncope or cardiac arrest before amiodarone therapy, and VT during predischarge ambulatory ECG monitoring. In this series, the predicted survival of patients who had these 3 variables was only 24% after 18 months of amiodarone therapy.

The following limitations require that the results of this study be examined with caution: (1) In our study, frequency of VPCs was classified qualitatively as frequent or infrequent. Frequency of quantitative VPCs may still have significant importance as a predictor of subsequent fatal and nonfatal events[15–18] not identified by this study. However, a consistent correlation has not been shown.[4,15–18] (2) Ejection fraction in 26 patients (30%) was determined by 2 dimensional echocardiography. Although this technique provides an objective measurement of left ventricular function, it is not as accurate as contrast or radionuclide ventriculography.[19]

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Results of Late Programmed Electrical Stimulation and Long-Term Electrophysiologic Effects of Amiodarone Therapy in Patients with Refractory Ventricular Tachycardia

ENRICO P. VELTRI, MD, PHILIP R. REID, MD, EDWARD V. PLATIA, MD, and LAWRENCE S.C. GRIFFITH, MD

Thirteen patients with refractory, recurrent, life-threatening ventricular tachycardia (VT) underwent electrophysiologic testing before and after long-term amiodarone therapy. Nine patients (69%) had coronary artery disease, 3 (23%) had nonischemic cardiomyopathy and 1 patient (8%) had mitral valve prolapse. At control electrophysiologic study, programmed electrical stimulation (PES) induced VT in all patients: sustained VT in 11 and nonsustained VT in 2 (9 beats and 31 beats). After oral loading with amiodarone, 1200 mg/day for 14 days, followed by maintenance therapy with 408 ± 20 mg/day (mean ± standard error of the mean), repeat PES at 6 ± 1.6 months revealed inducible VT in 12 of 13 patients: sustained VT in 11 and nonsustained VT (32 beats) in 1 patient. Inducible VT was suppressed in only 1 patient. Amiodarone significantly increased sinus cycle length, PR interval, QRS duration and right ventricular effective refractory period. Insignificant increases in AH, HV and QTc intervals were noted. At 24 ± 2 months, 8 patients (62%) (all with inducible VT at late PES) were free of clinical arrhythmic events (syncope or sudden death), compared with 5 patients (38%) (4 with inducible VT at late PES) with events. There were no significant differences in the induced VT cycle length, VT cycle length change, ease of inducibility or hemodynamic response to induced VT at late PES in patients with and without arrhythmic events. Thus, in patients who receive long-term amiodarone treatment, late PES does not predict clinical efficacy, the frequency of conversion from inducible VT to noninducible VT is low, and despite ventricular electrical instability as judged by late PES testing, amiodarone is clinically effective in patients at high risk.

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Amiodarone, a benzofuran derivative originally developed as an antianginal agent[1] and subsequently found to have potent antiarrhythmic properties,[2–4] is effective in ventricular tachyarrhythmias.[5–17] Many studies have revealed a disparity in clinical and electrophysiologic efficacy[12–15,18–21]; others suggest a predictive role of programmed electrical stimulation (PES) in patients with ventricular tachycardia (VT) treated with amiodarone.[22–24]

The discrepancies among previously reported PES studies (which, for the most part, were performed within 1 to 2 months of starting amiodarone therapy) as well as the unusual pharmacokinetic profile of the drug, namely an estimated half-life of many weeks,[25,26] prompted the investigation of the role of late (after 6 weeks) PES testing in predicting long-term clinical efficacy and the electrophysiologic effect of chronic amiodarone therapy.

From the Division of Cardiology, Department of Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland. This study was supported in part by General Clinical Research Center Grant RR00035-21 and the Outpatient General Clinical Research Center Grant RR00722-2, National Institutes of Health, Bethesda, Maryland. Manuscript received March 12, 1984; revised manuscript received September 17, 1984, accepted September 18, 1984.

Address for reprints: Philip R. Reid, MD, Sinai Hospital, Belvedere at Greenspring Avenue, Baltimore, Maryland 21215.

Methods

Patients: Thirteen patients (12 men, 1 woman) were referred to the Arrhythmia Service for the electrophysiologic evaluation of recurrent, life-threatening VT. Table I is a summary of the clinical characteristics. The mean age (± standard error of the mean) was 59 ± 4 years (range 22 to 74). All patients had at least 1 episode of documented sustained VT (mean 3.5). Twelve patients had 2 or more episodes within 1 year of referral. The clinical presentations were sudden death (cardiovascular collapse within 1 hour of symptoms requiring cardiopulmonary resuscitation or cardioversion from VT/ventricular fibrillation in the absence of acute myocardial infarction) in 9, syncope (transient loss of consciousness with spontaneous recovery) in 3, and presyn-

TABLE I Clinical Characteristics of the Patient Population (n = 13)

Male	12
Female	1
Age	59 ± 4
Ejection fraction	32 ± 4
Cardiac substrate	
CAD	9
CAD, MI	9
CAD, aneurysm	2
CCM	3
MVP	1
Clinical presentation	
Sudden death	9
Syncope	3
Presyncope	1
Previous drugs failed	5 ± 0.4
Amiodarone dose (mg/day)	
Loading	1,200
Maintenance	408 ± 20
Follow-up (mo)	24 ± 2

CAD = coronary artery disease; CCM = congestive cardiomyopathy; MI = myocardial infarction; MVP = mitral valve prolapse.

cope (light-headedness accompanying the arrhythmia) in 1 patient.

The underlying cardiac substrate, determined by cardiac catheterization and echocardiography, was coronary artery disease (defined by at least 70% coronary artery narrowing) in 9 patients (69%), nonischemic congestive cardiomyopathy (defined by diffuse left ventricular [LV] dysfunction with ejection fraction [EF] of 40% or less) in 3 patients (23%), and mitral valve prolapse in 1 patient (8%). Mean EF was 32 ± 4% (range 10 to 51%). All patients with coronary artery disease had previous myocardial infarction and 2 patients had LV aneurysm. In 11 patients, an automatic internal cardioverter-defibrillator (AICD, Intec Systems) had been placed. Treatment with 5 ± 0.4 previous drugs (range 3 to 8) had failed, defined as symptomatic arrhythmia recurrence, continued spontaneous VT on 24-hour Holter monitoring, VT induction by PES, or intolerable side effects from drugs. In all but 1 patient, treatment with at least 1 previous experimental antiarrhythmic agent (mean 1.6 drugs) had failed.

Electrophysiologic study: Control electrophysiologic study was performed after treatment with all antiarrhythmic agents (other than digoxin and β-blocking drugs) had been discontinued for 48 hours. Late PES (at least 6 weeks after amiodarone therapy started) was performed in all patients. All patients who received digoxin or β-blocking drugs during the control study continued to receive them to the time of late study.

Each patient gave informed consent for the study. Electrophysiologic studies were performed with the patient in the postabsorptive, nonsedated state. Standard quadripolar electrode catheters (10-mm interelectrode distance) were inserted through the femoral, brachial or subclavian veins; the right femoral artery was cannulated for hemodynamic monitoring and for LV stimulation if necessary. Programmed ventricular stimulation was performed using a digital stimulator that delivers rectangular pulses 1 ms in duration at twice diastolic threshold (less than 4 mA). Surface leads 1, avF, V_1, V_5 and intracardiac electrograms were simultaneously displayed on an oscillographic recorder (Electronics for Medicine VR-16). Analog data were displayed on a spray-ink recorder (Mingograf) for real-time analysis at paper speeds of 25, 50 and 100 mm/s and stored on magnetic tape for retrieval. Programmed ventricular stimulation was performed using single (S_1S_2) and double ($S_1S_2S_3$) extrastimuli at 3 basic ventricular pacing cycles (S_1S_1) (600, 500, 450 ms), followed by rapid ventricular decremental burst pacing (V_{burst}:10 consecutive beats at decreasing cycle lengths until 2:1 pacing noncapture). PES was performed in at least 2 right ventricular (RV) sites (apex and outflow tract) and 2 LV sites (apex, septum or anterolateral wall) if sustained VT was not induced. Refractory periods were measured at the same paced cycle length and site of stimulation before and after therapy for purpose of comparison.

TABLE II Results of Control and Late Programmed Electrical Stimulation in Patients Receiving Amiodarone Treatment

Control PES		Late PES	
10	Sustained VT	10	Sustained VT
1	Sustained VT	1	Noninducible
1	Nonsustained VT	1	Sustained VT
1	Nonsustained VT	1	Nonsustained VT

PES = programmed electrical stimulation; VT = ventricular tachycardia.

Definitions: *Nonsustained VT* was defined as VT that was reproducible (2 of 3 attempts) ≥ 3 repetitive ventricular beats that terminated spontaneously within 30 seconds and *sustained* VT as VT that lasted at least 30 seconds or required termination by ventricular overdrive pacing or external cardioversion due to hemodynamic compromise or degeneration into ventricular fibrillation. *Noninducibility* was defined as inability to induce VT at 2 RV and 2 LV sites using the protocol outlined above, and *ease of inducibility* was assessed by comparing the mode of extrastimulation and number of sites tested in control vs late PES testing. Easier induction required fewer extrastimuli (i.e., S_1S_2 vs $S_1S_2S_3$ vs V_{burst}) or fewer sites tested (i.e., RV apex vs RV apex + RV outflow tract, or RV site vs LV site) to induce VT.

Amiodarone administration: Physical examination, 12-lead electrocardiography, 24-hour Holter monitoring, complete blood count, basic chemistry screen including liver function tests, thyroid function tests, and ophthalmologic evaluation with slit-lamp examination were performed. All patients gave informed consent before amiodarone administration.

Twenty-four-hour Holter monitoring (Avionics model 445B) was performed using dual-channel recordings. The magnetic tapes were analyzed using a Del Mar Avionics model 660 Dynamic Electrocardio Scanner®. All tapes were reviewed by at least 2 of the investigators and VT was defined as at least 3 repetitive ventricular beats at a rate of more than 100 beats/min. The oral loading dose was 1,200 mg/day for 14 days and the maintenance dose ranged from 200 to 800 mg/day (mean 408 ± 20). In no patient was another antiarrhythmic agent added after control PES study.

Follow-up: Patients were followed in the Sudden Death Prevention Clinic at 2, 3, 4, 6, 9 and 12 months after discharge and every 6 months thereafter. Interim recurrent clinical arrhythmic events (syncope, sudden death or AICD discharge) and any adverse side effects were recorded. In cases of AICD discharge, the first discharge was considered a sudden death event for that patient. Physical examination, 12-lead ECG, 24-hour Holter, and repeat baseline blood studies were obtained at each visit. In addition, an external analyzer (AID CHECK, Intec Systems) was used to determine the number of AICD discharges delivered.

Amiodarone efficacy: We defined efficacy of amiodarone based on the absence of clinical arrhythmic events after starting amiodarone. Amiodarone was considered to be effective if the patient remained free of clinical arrhythmic event through follow-up.

Statistical analysis: The data are presented as mean ± standard error. Data were tested for significance by paired and unpaired Student t tests; a p value <0.05 was accepted as the limit of significance.

TABLE III Control and Late Electrophysiologic Variables in Seven Patients Treated with Amiodarone Alone

	Control	Late	p Value
RR	785 ± 50	895 ± 44	p <0.025
PR	173 ± 8	198 ± 11	p <0.005
QRS	99 ± 11	114 ± 13	p <0.05
QTc	441 ± 14	471 ± 20	NS
AH	100 ± 4	107 ± 8	NS
HV	57 ± 8	65 ± 5	NS
RV-ERP	250 ± 11	277 ± 14	p <0.025

All values are in milliseconds.
NS = not significant; RV-ERP = right ventricular effective refractory period.

Results

Control electrophysiologic study: At control electrophysiologic study, VT was induced in all patients: sustained VT in 11 and nonsustained VT in 2 (9 beats and 31 beats). The morphologic characteristics of the VT (bundle branch pattern and axis) were identical in all instances to the spontaneous clinical VT noted on 12-lead electrocardiogram or dual-channel Holter monitor. The induced VT cycle length ranged from 165 to 405 ms (mean 268 ± 16). Ten patients had VT induced on the right side (S_1S_2: 4; $S_1S_2S_3$: 4; V_{burst}: 2); in 3 patients VT was induced from the left ventricle (all using $S_1S_2S_3$ mode).

Late electrophysiologic study: Late PES testing was performed in all patients at 6 ± 1.6 months (range 6 weeks to 15 months) after starting amiodarone. VT was induced in 12 patients: sustained VT in 11 and nonsustained (32 beats) in 1 patient. Again, in all instances the morphologic characteristics of the VT were identical to the spontaneous clinical VT. The induced VT cycle length ranged from 202 to 465 ms (mean 324 ± 21). Ten patients had VT induced on the right side (S_1S_2: 2; $S_1S_2S_3$: 6; V_{burst}: 2) and 2 patients required left ventricular stimulation to induce VT (both using $S_1S_2S_3$ mode).

Table II is a summary of the results at both control and late PES. Of the 11 patients with inducible sustained VT at control study, only 1 patient had VT suppressed at late PES. One patient with inducible nonsustained VT (31 beats) at control study had sustained VT induced at late study. The other patient with inducible nonsustained VT (9 beats) at control study had nonsustained VT (32 beats) induced at late study.

The VT cycle length at late study compared to control study was significantly increased (324 ± 21 vs 268 ± 16 ms, p <0.005). The VT cycle length was increased in 10 patients, decreased in 1 and unchanged in 1. The mean VT cycle length change was +70 ms (range −88 to 140 ms). Based on our criteria for ease of inducibility, inducibility was unchanged in 4, easier in 4 and more difficult in 4.

The hemodynamic response (systolic blood pressure) to induced VT was significantly improved at late study compared to control study (61 ± 12 vs 48 ± 12 mm Hg, p < 0.05).

Chronic electrophysiologic effects: There were 7 patients treated with amiodarone alone (no digoxin or β-blocking drugs) in whom intracardiac conduction times and RV effective refractory periods (ERP) at control and late study could be compared. Table III is a summary of the findings. Amiodarone significantly increased sinus cycle length (RR), PR interval, QRS duration and RVERP.

TABLE IV Comparison of Patients With and Without Clinical Arrhythmic Events

	Nonevent	Event	p Value
No. of pts	8	5	
Ejection fraction	30 ± 5	36 ± 5	NS
Inducible VT (late PES)	8	4	
VT cycle length (late PES)	333 ± 20	311 ± 52	NS
VT cycle length change	65 ± 16	85 ± 22	NS
Systolic BP response to VT (control PES)	50 ± 16	43 ± 19	NS
Systolic BP response to VT (late PES)	65 ± 15	53 ±11	NS
Change in RVERP	24 ± 5	20 ± 3	NS
Ease of VT inducibility			
Unchanged	3	1	
Easier	2	2	
More difficult	3	1	

BP = blood pressure; NS = not significant; PES = programmed electrical stimulation; RVERP = right ventricular refractory period; VT = ventricular tachycardia.

Holter monitoring: All patients had documented spontaneous nonsustained VT when not receiving antiarrhythmic agents (other than digoxin and β-blocking drugs) on the baseline 24-hour Holter recording. Patients had 9.7 ± 1.2 twenty-four-hour Holter recordings after 1 week of therapy through follow-up. Spontaneous nonsustained VT was completely suppressed in 7 patients (54%). Three patients without subsequent clinical arrhythmic events had nonsustained VT on any follow-up Holter (4 of 30 total Holter recordings). Three patients with subsequent events had nonsustained VT on any follow-up Holter (8 of 34 total Holter recordings). In each instance, nonsustained VT was 3 to 10 beats and asymptomatic.

Clinical efficacy: At 24 ± 2 months of follow-up (range 4 to 38), 8 patients (62%) were free of clinical arrhythmic events. All of these patients had inducible sustained VT at both control and late PES. Of the 5 patients (38%) with clinical arrhythmic events, 4 had inducible VT (3 sustained VT, 1 nonsustained VT) at late study. Clinical arrhythmic events manifested as recurrent sudden death in 4 patients (3 had AICD discharges with successful cardioversion-defibrillation) and syncope in 1 patient. Of the 11 patients with inducible sustained VT at late study, only 3 patients (27%) had clinical arrhythmic events.

Table IV is a summary of the findings in patients with and without clinical arrhythmic events. There were no significant differences in VT cycle length, VT cycle length change, ease of VT inducibility, or hemodynamic response to induced VT at late PES in patients with or without arrhythmic events. Likewise, there were no significant differences in these variables in a subset analysis that excluded patients with inducible nonsustained VT at either control or late PES.

Nine patients (69%) were alive at follow-up. Four patients died: 2 suddenly and 2 from refractory heart failure. The mean EF in the surviving patients was significantly better than that in patients who died, 37

TABLE V Comparison of Programmed Electrical Stimulation Studies in Patients Receiving Amiodarone Treatment

	No. of Pts	PES	Inducible	Follow-Up	Events*
Heger et al[12]	19	2–4 wk	18 (95%)	12.7 mo	6 (33%)
Waxman et al[13]	43	2–108 days	38 (88%)	8.6 mo	23 (50%)†
Nademanee et al[14]	30	2 wk	14 (47%)	15.0 mo	0
Haffajee et al[15]	20	3–34 wk	11 (55%)	6.8 mo	3 (27%)
Hamer et al[18]	9	7–20 wk	7 (78%)	15.0 mo	0
Nademanee et al[19]	13	14–56 days	4 (31%)	12.0 mo	0
Waxman[20]	58	7–210 days	50 (86%)	12.0 mo	26 (52%)
Groh et al[21]	10	?	4 (40%)	2–9 mo	0
McGovern & Ruskin[22]	30	8–42 days	14 (47%)	12.5 mo	8 (57%)‡
Saksena et al[23]	10	21–88 days	1 (10%)	3.5 mo	0
Saksena et al[24]	24	21–81 days	12 (50%)	2.5–20 mo	6 (50%)§
Present study	13	1.5–15 mo	12 (92%)	24 mo	4 (33%)

* Number and percent of patients in whom VT could be induced with clinical arrhythmic events.
† Represents patients with clinical arrhythmic events of total population.
‡ Represents only patients who had VT as easily or more easily induced compared to control study.
§ Includes 5 patients who had clinical VT recurrence and 1 patient who had morphologically new arrhythmia induced.
PES = programmed electrical stimulation; VT = ventricular tachycardia.

± 3% vs 19.5 ± 5% ($p < 0.01$). A significant difference remained if the 3 patients with resuscitated sudden deaths were included as patients dead at follow-up.

Side effects: Significant side effects were noted in 4 patients (31%); 1 patient (8%) required drug withdrawal. Two patients had asymptomatic elevated liver function tests manifested by 2 to 3-fold elevations in transaminases and concomitant elevated thyroid function tests; 1 patient underwent permanent pacemaker insertion due to symptomatic sinus bradycardia. In 1 patient, a progressive sensory-motor neuropathy developed.

Discussion

Role of programmed electrical stimulation: The ability of certain antiarrhythmic agents to prevent the induction of VT in patients with recurrent VT is predictive of the drug efficacy in eliminating spontaneous recurrences during short-term and long-term therapy.[28–30] Conversely, induction of sustained ventricular tachyarrhythmias during conventional type I antiarrhythmic drug therapy by PES predicts recurrence of clinical arrhythmia. In the case of amiodarone, most studies have revealed a disparity between electrophysiologic and clinical efficacy,[12–15,18–21] whereas others have suggested a predictive role of PES.[22–24]

Our study supports the discrepancy in clinical and electrophysiologic efficacy of amiodarone. In this series, electrophysiologic study was performed more than 6 weeks (mean 6 months) after starting amiodarone, which is 3 to 6 times longer than previous studies and well into the projected steady-state period.

Table V is a summary of the results of previous studies in comparison to the present study. Twelve of 13 patients (92%) had inducible VT at late PES testing. This is similar to the findings of Heger et al,[12] Hamer et al,[18] and Waxman,[20] but is somewhat higher than that reported by others.[14,15,19,21–24]

At 24 ± 2 months of follow-up only 4 of 12 patients (33%) with inducible VT at late PES had had recurrent clinical arrhythmic events. This is similar to the 33% and 27% reported by Heger et al[12] and Haffajee et al,[15] respectively. In our series, only 3 of 11 patients with inducible sustained VT at late PES had clinical arrhythmic events. Similarly, only 2 of 10 patients with inducible sustained VT at both control and late PES studies had events. The only converter from inducible VT to noninducible in our series had recurrent spontaneous VT with syncope at 15 months of therapy.

Although we have reported AICD discharges during supraventricular tachyarrhythmias,[31] none of the patients with AICD discharges in the present study had histories of supraventricular tachyarrhythmias and the premonitory symptoms before AICD discharge were always similar to previous episodes of VT. Thus, we feel that AICD discharge was justified as an endpoint event.

McGovern and Ruskin,[22] using a grading system similar to ours to determine the ease of VT inducibility, reported that long-term clinical outcome was predicted by the PES results in 77% of patients. In the present study, the ease of VT induction was variable in patients with and without events and, thus, was not predictive. This is in agreement with the findings of Waxman et al,[13] who demonstrated the failure of amiodarone to alter the ease of VT induction in any consistent fashion at shorter follow-up study time.

Amiodarone lengthens the action potential duration, prolongs refractoriness and slows impulse conduction in ventricular myocardium.[3] As noted in earlier studies, the VT cycle length in most patients was prolonged. Similarly, the RVERP was lengthened by 11%, which is within the 8 to 23% range noted previously.[12–14,18,19,22,24,27,32] However, there were no significant differences in VT cycle length, VT cycle length change, or RVERP change comparing patients with and without clinical arrhythmic events at follow-up. Therefore, amiodarone clearly has effects on electrophysiologic characteristics of ventricular tissue and on the induced VT rate, but these effects do not appear to correlate with clinical outcome. This leads to the speculation that most patients still have the vulnerability for sustained VT, but that the protective mechanism may lie in suppression of ventricular ectopic activity or abolition of triggers that initiate clinically important ventricular arrhythmias.

Although nonclinical morphologic forms of ventricular tachyarrhythmias in addition to the clinical spontaneous forms can be induced by PES,[33] in our series only clinical VT morphologic patterns were induced. This is in contrast to the findings of Saksena et al,[24] who reported that in 42% of patients receiving chronic amiodarone therapy, morphologically new ventricular tachyarrhythmias were induced by PES. These investigators used a much more aggressive stimulation protocol.

Differences in patient populations, amiodarone loading and maintenance dosage, interval between control and follow-up electrophysiologic study, programmed stimulation protocols, and definitions of induced VT may account for the discrepancies between our PES findings and those of previous studies.

Clinical efficacy: At 24 ± 2 month follow-up, 62% of the patients were free of clinical arrhythmic events. This degree of efficacy concurs with that of most previous studies,[6,9,10–13,16] but is somewhat less than that reported by others.[5,7,8,14,15] Again, discrepancies in efficacy can be accounted by differences in patient populations, drug dosage, duration of therapy, and definitions of efficacy. Our patients had a mean 3.5 episodes of sustained VT in the year preceding referral and 92% had failed at least 1 previous experimental agent (mean 1.6). Thus, the efficacy rate of 62% may reflect the response in a group of patients at exceptionally high risk.

Although overall LV function (EF) did not predict clinical arrhythmic events, the mean EF certainly was worse in patients who later died from a cardiac cause. This concurs with the findings of Swerdlow et al,[34] who reported overall LV function as an important determinant of survival from cardiac death in patients with ventricular tachyarrhythmias.

Side effects: In our series, significant side effects were noted in 31% of patients, yet only 8% required drug withdrawal. These findings are consistent with most previous studies.[5–8,10–12,14,15]

Conclusions: We conclude that although amiodarone is an effective, fairly well-tolerated antiarrhythmic agent in patients with refractory, recurrent VT, late PES testing does not predict clinical efficacy. Indeed, the frequency of conversion from inducible VT to noninducible VT is low. Further insight into the protective action of amiodarone may be achieved by efforts aimed at understanding the triggering mechanisms for onset of spontaneous ventricular tachyarrhythmias.

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Comparison in the Same Patient of Two Programmed Ventricular Stimulation Protocols to Induce Ventricular Tachycardia

PEDRO BRUGADA, MD, and HEIN J. J. WELLENS, MD

In 24 consecutive patients with documented ventricular tachycardia (VT) (22 patients) or fibrillation (VF) (2 patients), results of 2 programmed ventricular stimulation protocols to initiate VT/VF were prospectively studied. Seventeen patients had VT/VF after a healed myocardial infarction (MI) and 7 patients had idiopathic VT. In both protocols (designated 1 and 2), the right ventricular (RV) apex was paced at 100 beats/min, using a maximum of 2 ventricular premature complexes (VPCs) given at twice diastolic threshold. This protocol had a sensitivity of 25%. In protocol 1, the pacing site was changed to the RV outflow tract and the previous steps were repeated; in protocol 2, the pacing rate was increased to 120 and 140 beats/min at the RV apex, also using a maximum of 2 VPCs. The next step in protocol 1 consisted of increase of current strength to 20 mA and repeating previous steps at the RV apex and RV outflow tract, with a maximum of 2 VPCs; in the next step in protocol 2, three VPCs were used during sinus rhythm and pacing was performed at rates of 100, 120 and 140 beats/min. In protocol 1, therefore, only stimulation site and current strength were changed, while in protocol 2 only pacing rate and number of VPCs were modified. Protocol 1 had a sensitivity of 54% and protocol 2 a sensitivity of 83%. The sensitivity of protocol 2 was statistically higher than that of protocol 1 ($p < 0.05$). In the group of patients with VT after MI, the sensitivity was 66% for protocol 1 and 93% for protocol 2. Protocol 2 combined with administration of isoproterenol had a sensitivity of 95% (100% in the patients with VT after MI).

These observations have important implications for the design of the most successful order of programmed ventricular stimulation in patients with documented VT/VF. If stimulation at the RV apex using a single pacing rate and 2 VPCs given at twice threshold fail to initiate VT, increase of pacing rate and, thereafter, use of 3 VPCs is a much more effective means of initiating VT than changing the stimulation site to RV outflow tract or increasing the current strength to 20 mA.

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Programmed electrical stimulation of the heart was introduced in clinical cardiology in 1967.[1,2] Since then, the technique has gained wide acceptance for studying patients with supraventricular or ventricular arrhythmias. The initial studies showed that some tachycardias could be easily reproduced by this technique; other tachycardias could not be induced or only rarely induced.[3–7]

With the introduction of programmed stimulation in clinical cardiology, an ever-growing variety of stimulation protocols became available. This is troublesome when trying to understand results of programmed stimulation in patients with documented ventricular tachycardia (VT) or fibrillation (VF) or when trying to identify patients at risk of arrhythmic complications.[8–10] In patients with electrocardiographically well documented VT or VF, programmed stimulation is used to understand modes of initiation and termination of the arrhythmia, its site or origin and pathways, possible mechanisms, and to study the effect of antiarrhythmic therapy on the tachycardia mechanisms. Programmed stimulation should reproduce the arrhythmia rapidly and effectively. To determine the sensitivity of different ventricular stimulation protocols, a prospective study was undertaken comparing 2 different protocols in the same patient.

From the Department of Cardiology, University of Limburg, Annadal Hospital, Maastricht, The Netherlands. Manuscript received September 14, 1984; revised manuscript received October 29, 1984, accepted October 30, 1984.

Address for reprints: Pedro Brugada, MD, Clinical Electrophysiology Laboratory, University of Limburg, Department of Cardiology, Annadal Hospital, Maastricht, The Netherlands.

Methods

Twenty-four consecutive patients were studied by programmed ventricular stimulation. All gave informed consent

TABLE I Pacing Modalities Used in Protocol 1 and Protocol 2

Steps	Protocol 1	Protocol 2
First	Common	Common
Second	Change pacing site	Increase pacing rate
Third	Increase current strength	Increase number VPCs

VPC = ventricular premature complex.

TABLE II Mode of Initiation of Ventricular Tachycardia/Fibrillation in 24 Patients

Mode of Initiation	VT/VF-MI	VT Idiopathic
Ventricular stimulation alone	16/17	4/7
Isoproterenol alone	0/1	2/3
Isoproterenol and ventricular stimulation	1/1	0/1
VT not initiated	0/17	1/7

VT = ventricular tachycardia; VT/VF-MI = ventricular tachycardia/fibrillation after myocardial infarction.

and none was receiving antiarrhythmic drug treatment. Twenty-two patients had documented sustained VT and 2 patients documented VF. VT or VF occurred without relation to a new ischemic event in these patients. Seventeen patients had a healed MI (VT-MI) and 7 patients had idiopathic VT.

Methods of stimulation, recording and analysis of tracings have been described.[3] Electrode catheters were placed at the right atrium, right ventricular (RV) apex, RV outflow tract and His bundle area. To compare results of the 2 protocols, VT or VF was initiated at least twice in each patient. The study was terminated immediately, however, when the patient required 2 direct-current countershocks to terminate VT or VF resulting in loss of consciousness.

Two protocols were used on each patient.

Protocol 1: Protocol 1 consisted of 8 steps: (1) 1 ventricular premature complex (VPC) given at the RV apex during pacing at a rate of 100 beats/min at twice threshold; (2) 2 VPCs given at the RV apex during pacing at 100/beats/min at twice threshold; (3) 1 VPC given at the RV outflow tract during pacing at 100 beats/min at twice threshold; (4) 2 VPCs given at the RV outflow tract during pacing at 100 beats/min at twice threshold; (5) 1 VPC given at the RV apex during pacing at 100 beats/min using 20 mA; (6) 2 VPCs given at the RV apex during pacing at 100 beats/min using 20 mA; (7) 1 VPC given at the RV outflow tract during pacing at 100 beats/min using 20 mA; and (8) 2 VPCs given at the RV outflow tract during pacing at 100 beats/min using 20 mA.

Protocol 2: Protocol 2 consisted of 12 steps: (1) 1 VPC given at the RV apex during sinus rhythm at twice threshold; (2) 2 VPCs given at the RV apex during sinus rhythm at twice threshold; (3) 1 VPC given at the RV apex during pacing at 100 beats/min at twice threshold; (4) 2 VPCs given at the RV apex during pacing at 100 beats/min at twice threshold; (5) 1 VPC given at the RV apex during pacing at 120 beats/min at twice threshold; (6) 2 VPCs given at the RV apex during pacing at 120 beats/min at twice threshold; (7) 1 VPC given at the RV apex during pacing at 140 beats/min at twice threshold; (8) 2 VPCs given at the RV apex during pacing at 140 beats/min at twice threshold; (9) 3 VPCs given during sinus rhythm at the RV apex at twice threshold; (10) 3 VPCs given at the RV apex during pacing at 100 beats/min at twice threshold; (11) 3 VPCs given at the RV apex during pacing at 120 beats/min at twice threshold; and (12) 3 VPCs given at the RV apex during pacing at 140 beats/min at twice threshold.

All stimuli were bipolar and had a duration of 2 ms both in protocols. Diastolic thresholds were less than 1.5 mA. In only 1 patient was VT initiated by giving 1 and 2 VPCs during sinus rhythm. In that patient, VT was also initiated by giving 1 VPC during pacing at the RV apex at a rate of 100 beats/min. This allowed us to compare the results of protocol 1 and protocol 2 after an initial common step, which consisted of pacing at the RV apex at 100 beats/min using a current strength of twice threshold and up to 2 VPCs. After this common step, pacing site was changed to the RV outflow tract in protocol 1, whereas stimulation was continued from the RV apex and the pacing rate was increased in protocol 2. The next step in protocol 1 was an increase of current strength to 20 mA, whereas the number of VPCs was increased in protocol 2. These steps are summarized in Table I. When stimulation was completed and if VT had not been initiated, isoproterenol was given intravenously to produce an acceleration in sinus rate of 20%. If isoproterenol alone did not induce VT, stimulation was repeated under isoproterenol using the same sequence as previously described. Results obtained during administration of isoproterenol, however, were not included to evaluate results of protocol 1 or protocol 2. Using our simultaneous recording of many electrocardiographic leads, only ventricular arrhythmias similar to those clinically documented were used for evaluation of results. Nonsustained VT was not considered the clinical ventricular arrhythmia in any of these patients, who all suffered from sustained ventricular arrhythmias (lasting longer than 30 seconds or producing loss of consciousness). Other definitions to classify the different types of ventricular arrhythmias used in our laboratory have been described.[11,12] Statistical analysis was performed using the chi-square test.

Results

Table II is a summary of the mode of initiation of VT in the 24 patients, in relation to the cause of VT. The clinical ventricular arrhythmia was initiated by ventricular stimulation in all but 1 patient in the VT-MI group. In that patient, VT was initiated by stimulating during intravenous administration of isoproterenol. VT was initiated by ventricular stimulation in 4 of 7 patients in the idiopathic-VT group. In 2 of the 3 other patients in this group, VT was initiated by isoproterenol without need for electrical stimulation. In the remaining patient, VT could not be induced. Twenty-two patients underwent a complete stimulation study using protocol 1 and 23 patients underwent a complete stimulation study using protocol 2. The reasons for not completing the protocols were repeat cardioversions in 1 patient and chest pain during 20-mA stimulation in the other 2.

Figure 1 illustrates the sensitivity of protocols 1 and 2 in patients in the VT-MI group. The earliest step in the program that resulted in initiation of sustained VT was considered for analysis of sensitivity. Protocol 1 had a sensitivity of 66% and protocol 2 a sensitivity of 93%. When sensitivity of these protocols were compared only for the VT-MI group, results were not statistically significant ($\chi^2 = 3.6382$, $0.05 < p < 0.1$). When the whole population of patients was considered, however, protocol 2 had a sensitivity of 83%, which was significantly higher than that of protocol 1 (54%) ($p < 0.05$).

Figure 1 illustrates another important point. Stimulation was more extensive during protocol 2 than protocol 1. Therefore, it was important to know whether, protocol 2, included more ineffective steps

than protocol 1. There were 120 possible steps for the 15 patients of the VT-MI group in protocol 1, compared with 180 possible steps for the 16 patients of the same group when using protocol 2. In protocol 1, 74 steps were ineffective to initiate VT (relative inefficacy 0.62), and in protocol 2, 97 steps were ineffective (relative inefficacy 0.56, a value of 1.0 indicating a completely ineffective program). These results shows that protocol 2 markedly increased sensitivity to initiate VT, without increasing the relative number of ineffective stimulation steps, compared to protocol 1.

Results of protocol 1 and protocol 2 can also be illustrated, as in Figure 2, by considering changes in pacing modality that each program contained. A pacing protocol using up to 2 VPCs given at twice threshold during pacing at the RV apex at 100 beats/min was taken as initial common step for both protocols. This step had a sensitivity of 25%. A change in pacing site to the RV outflow tract in protocol 1 increased sensitivity to 33%, and an increase of current strength to 20 mA increased sensitivity to 66%. Using the steps of protocol 2 however, by simply increasing the pacing rate, sensitivity increased to 68%, which was higher than the sensitivity reached by the entire protocol 1. Thereafter, by using 3 VPCs during sinus rhythm and ventricular pacing, a sensitivity of 81 and 93% was reached with protocol 2.

Isoproterenol: Results of administration of isoproterenol were not considered for evaluation of sensitivity of either protocol because patients in whom VT was not induced by protocol 1 but in whom it was induced by protocol 2 did not receive isoproterenol. When results with isoproterenol were added to results of protocol 2, however, sensitivity increased to 95% for the whole patient population and to 100% in the VT-MI group.

Discussion

When using programmed ventricular stimulation in patients with well documented VT or VF, the most important aspect of the protocol is its sensitivity in reproducing VT, rather than specificity. Electrical stimulation should reproduce VT rapidly and effectively. Specificity of electrical stimulation becomes of major importance, however, when patients with no documented VT undergo programmed ventricular stimulation either to clarify symptoms suggesting arrhythmias or to identify patients at high risk of arrhythmic complications. We have extensively discussed elsewhere that specificity of electrical stimulation can be markedly improved when not only the mode of initiation of VT is considered but also the type of arrhythmia initiated is carefully analyzed.[11,12]

In this study 2 protocols were compared in the same patient. We preferred this approach to a randomized study because we did require initiation of VT in all patients with documented VT. When patients would have been randomized, we had the risk of not inducing VT in a significant percentage of patients randomized to 1 of the 2 protocols. When VT would have not been induced we would have been unable to proceed further in the evaluation of these patients by programmed stimulation. Therefore, we used both protocols in all patients, and let the patient serve as his own control. The

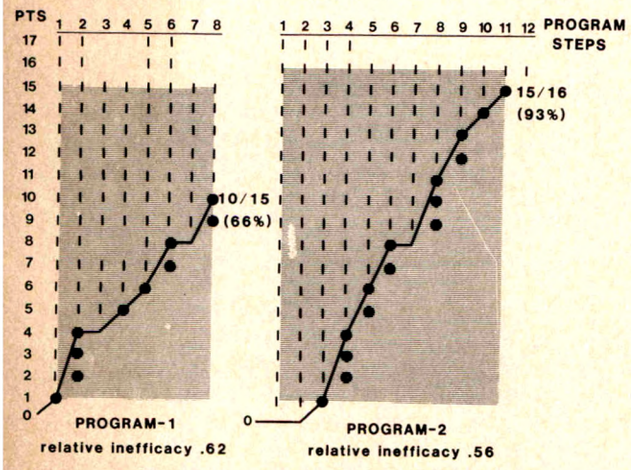

FIGURE 1. Sensitivity of protocols 1 and 2 in the patients with ventricular tachycardia/fibrillation after myocardial infarction. The steps of each protocol are shown at the **top** (8 steps for protocol 1 and 12 steps for protocol 2. Each **vertical line** indicates a particular stimulation step. Two patients did not complete protocol 1 and 1 patient did not complete protocol 2. The **dots** indicate the earliest step during each protocol resulting in initiation of sustained ventricular tachycardia. The **dashed area** represents the total possible stimulation steps in each protocol, and indicates that protocol 2 was more extensive than protocol 1. The relative inefficacy of the 2 protocols was, however, similar (0.62 and 0.56). Protocol 1 reached a sensitivity of 66% and protocol 2 a sensitivity of 93%.

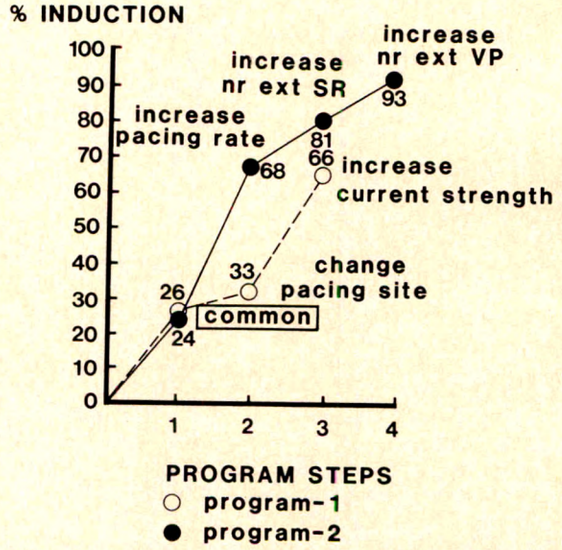

FIGURE 2. Sensitivity of protocols 1 and 2 in the group of patients with ventricular tachycardia/fibrillation after myocardial infarction by considering the different pacing modalities used during each protocol. After a common step that used a single pacing rate and 2 ventricular premature complexes (VPCs) given at twice threshold at the right ventricular apex (sensitivity 25%), increase in pacing rate and use of 3 VPCs was more effective in initiating VT than change in pacing site or increase of current strength to 20 mA. Nr ext = number of VPCs; SR = sinus rhythm; VP = ventricular pacing.

results showed that protocol 2 had a much higher sensitivity than protocol 1 in reproducing VT.

Relevance for the design of standard ventricular stimulation protocols: A standardized protocol used order by all groups performing electrical stimulation studies would facilitate understanding of results of programmed stimulation in different patient populations. Richards et al[13] reported a protocol identical to protocol 1 of our study. They reported a sensitivity of 89% in a series of 27 patients with documented VT/VF. In the 24 patients that we studied prospectively, this high sensitivity could not be confirmed. There are several reasons for this, including the definitions used to classify a study as positive. Richards et al used a cutoff point of 10 seconds to consider a ventricular arrhythmia as sustained, and they did not classify the types of ventricular arrhythmias initiated. In our study only ventricular arrhythmias such as those suffered clinically by the patient, and lasting at least 30 seconds, were considered as a positive result. Richards et al[9] also reported a specificity of 100% for the same protocol to identify patients after MI prone to develop VT or sudden death. While the positive predictive value of their protocol was extremely low (26%), the value of programmed electrical stimulation to identify candidates to arrhythmic complications after MI has not been confirmed.[10] Sensitivity of programmed stimulation in patients with documented sustained VT or VF using a pacing protocol similar to our protocol 2 has been greater than 80% in other laboratories.[14–17] This sensitivity was confirmed in the present study.

Morady et al[18] reported a study of programmed ventricular stimulation. They compared triple stimuli to left ventricular stimulation in 2 groups of patients. Although the patients were not randomized, the clinical data of the 2 groups were similar. Morady et al concluded that the initial use of burst overdrive pacing and single and double extrastimuli in the right ventricle can obviate need for triple extrastimuli in 53% of patients. However, one must realize that this pacing protocol also included stimulation in the RV outflow tract or RV septum in addition to stimulation at the RV apex. Morady et al also concluded that triple extrastimuli were required in 24% of patients. They did not report results regarding the relative inefficacy of their protocols A and B. This is important because the sensitivity of our protocol 2 was similar to that of their protocol. Their protocol had 33 steps. How many of these steps were undertaken and were ineffective to reproduce VT remains unknown from the data they reported.

The difficulties of our prospective study comparing 2 protocols in the *same* patient should not be underestimated. Initiation of VT at least twice was necessary in each patient, including those who required external direct-current countershock to terminate VT. Despite the small size of our study group, the differences between protocol 1 and protocol 2 were statistically significant, and the study was terminated.

In conclusion, we suggest that when a stimulation protocol using up to 2 VPCs from the RV apex at twice threshold during pacing at 100 beats/min fails to initiate VT, increase of the pacing rate using 3 VPCs during sinus rhythm and ventricular pacing is a more effective means of initiating VT than change of pacing site to RV outflow tract or increase of current strength to 20 mA. Administration of isoproterenol and stimulation during isoproterenol can further increase sensitivity of programmed stimulation.

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Late Potentials in Normal Subjects and in Patients with Ventricular Tachycardia Unrelated to Myocardial Infarction

HUMBERTO COTO, MD, CLAUDIO MALDONADO, MA, PRASAD PALAKURTHY, MD, and NANCY C. FLOWERS, MD

Fifty normal male and female athletes, or athletically active subjects, were evaluated, and a search for low-amplitude late potentials in the terminal part of ventricular activation was performed. Recordings from 3 normal men met the definition of abnormal late potentials, and were indistinguishable by present analytic techniques from those encountered in patients who have ventricular tachycardia (VT) after myocardial infarction (MI). Of 24 patients studied, 11 had VT, but only 2 had had an MI, which occurred in the remote past. Another patient had 1 narrowed coronary artery on arteriography. Group differences could be demonstrated using amplitudes and durations of late potentials, but late potentials generally did not prove the impressive marker of the patient with VT, which other workers, as well as ourselves, have encountered in patients after MI. Late potentials were an impressive marker in a subset of the VT group in whom cardiomegaly developed. Thus, the absence of late potentials is an effective marker in the normal subject, but the presence of late potentials is not an effective marker in identifying the patient with non-MI-related, nonsustained VT before development of cardiomegaly.

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In 1973, Boineau and Cox[1] demonstrated slow ventricular activation, in association with a recent myocardial infarction (MI), as a source of reentrant premature ventricular depolarizations. Berbari et al[2] reported arrhythmogenic ventricular activity occurring during the ST segment in 1978. In the early 1980s, Simson,[3] Breithardt et al[4] and, more recently, other investigators, evaluated late potentials as a possible means of identifying certain patients prone to ventricular tachycardia (VT). Late potentials may be thought of as deflections occurring after the dominant QRS-wave form that are relatively high in frequency and too low in amplitude to be distinguishable from noise without the application of additional noise reduction and signal enhancing techniques such as amplification, filtering and signal averaging. Based on either the duration of relatively low amplitude deflections in the terminal QRS or the ST segment, or the determination of the root-mean-square (RMS) of the voltage over a particular time period after the basic QRS wave form, certain group and possibly individual differences may be shown between those patients who sustained MI and later had VT and those who did not. One difficulty in extending these initial nosologic observations further is the scarcity of information on the incidence of low-amplitude late potentials in normal subjects.[5] Our study characterizes the occurrence of late potentials in a normal and athletically active group who had not sought entry into a health care system, and evaluates the predictive accuracy of late potentials in distinguishing another population subset with VT from causes other than MI.

From the Division of Cardiology, University of Louisville, Louisville, Kentucky, and the Division of Cardiology, Medical College of Georgia, Augusta, Georgia. This study was supported by Grant HL 33692 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received June 14, 1984; revised manuscript received October 15, 1984, accepted October 16, 1984.

Address for reprints: Nancy C. Flowers, MD, Professor of Medicine, Division of Cardiology, Medical College of Georgia, Augusta, Georgia 30912.

Methods

Fifty normal subjects, all of whom either were athletes (n = 38) or exercised regularly (n = 12), were studied. Before inclusion into the study, each subject had a cardiovascular history taken and underwent physical evaluation, including a detailed smoking and family history. None were included who had a family history of early heart disease or who smoked in excess of 10 cigarettes daily. All subjects had a normal routine electrocardiogram (ECG). The ages of the 26 men and 24 women ranged from 18 to 36 years (mean 25.0 ± 5.8).

An additional 24 patients, recently referred for problems relating to cardiac rhythm or conduction, were considered for the study. One patient had right bundle branch block with a standard QRS duration of 130 ms. Another patient had an intraventricular conduction defect with a QRS of 140 ms. All other patients had standard QRS durations less than 120 ms. Eleven with nonsustained VT will be considered in this report. Each was symptomatic, had repetitive episodes, and therapy was required for control. All of the 11 had episodes that

stopped within 30 seconds, and all had demonstrated at least a 5-beat salvo. One patient had an occasional episode (by definition a sustained VT), lasting longer than 30 seconds. No patient had acute MI and only 2 had remote MI. Another patient had an occlusion larger than 75%, visualized in 1 coronary artery and 1 had insignificant plaque formation. The remaining causes were specifically not coronary artery disease and included mitral valve prolapse, idiopathic dilated cardiomyopathy, overdosage of Mellaril® in 1 patient, essential hypertension and aortic valve disease.

The recording and signal-averaging process was performed with a system from Arrhythmia Research Technology which uses essentially the instrumentation described by, and the software developed by, Simson et al.[3,6] In many instances, normal subjects and patients were recorded on more than 1 occasion to verify stability. In brief, 3 relatively orthogonal sampling points were amplified at a gain of 1,000, with a band width of 0.05 to 300 Hz, with a noise level of 0.7 μV referred to input. The signal from each lead was further amplified 5 times and passed through a 4-pole, 250-Hz low-pass filter. Analog-to-digital conversion was performed to 12-bit accuracy at a sampling rate of 1,000/s on a Hewlett-Packard 9826 computer, and the information was stored on floppy disks. Each lead was recorded for $2\frac{1}{2}$ minutes. With the Z lead as temporal reference lead, an 8-point template began at a reference time and extended for 128 ms to include distal QRS and early ST segment. The initial 8-beat template was accepted if the mean standard deviation after direct current shift was under 20 μV. Subsequent beats were tested against the template and accepted when within twice template standard deviation. During averaging, a 512-ms segment of the heart beat was identified, beginning 100 ms before onset of the QRS, and the template updated every fourth beat. After averaging, the records were filtered to eliminate low frequencies using a high-pass filter (HPF) at both 25 and 50 Hz in the present protocol. A bidirectional digital filter modified by Simson et al[6] that achieves the elimination of ringing was used. The filtered signals for the X, Y and Z leads were integrated into a vectormagnitude complex by the usual formula, $M = \sqrt{X^2 + Y^2 + Z^2}$. Onset and offset of QRS were determined by computer algorithm, by respective forward and backward searches noise level to determine the midpoint of the 5-ms segment in which the average signal exceeds the noise level mean ±3 standard deviations.

Measurements included the total duration of the integrated QRS complex, the total duration of the terminal QRS potentials that are less than 40 μV RMS, the total duration of potentials in terminal QRS less than 25 μV RMS, the RMS of the total voltage in the last 40 and the last 50 ms of the QRS.

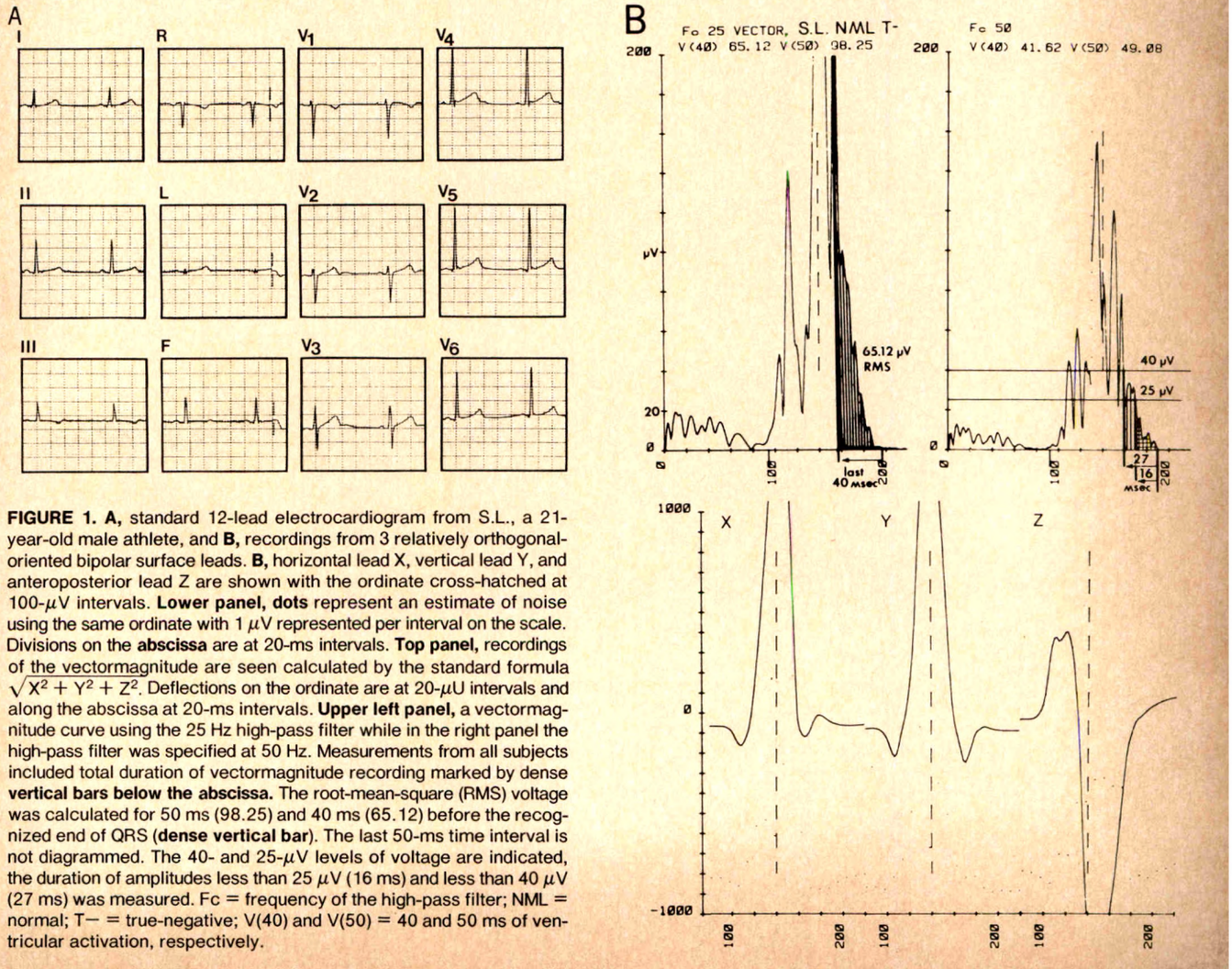


FIGURE 1. A, standard 12-lead electrocardiogram from S.L., a 21-year-old male athlete, and **B,** recordings from 3 relatively orthogonal-oriented bipolar surface leads. **B,** horizontal lead X, vertical lead Y, and anteroposterior lead Z are shown with the ordinate cross-hatched at 100-μV intervals. **Lower panel, dots** represent an estimate of noise using the same ordinate with 1 μV represented per interval on the scale. Divisions on the **abscissa** are at 20-ms intervals. **Top panel,** recordings of the vectormagnitude are seen calculated by the standard formula $\sqrt{X^2 + Y^2 + Z^2}$. Deflections on the ordinate are at 20-μU intervals and along the abscissa at 20-ms intervals. **Upper left panel,** a vectormagnitude curve using the 25 Hz high-pass filter while in the right panel the high-pass filter was specified at 50 Hz. Measurements from all subjects included total duration of vectormagnitude recording marked by dense **vertical bars below the abscissa.** The root-mean-square (RMS) voltage was calculated for 50 ms (98.25) and 40 ms (65.12) before the recognized end of QRS (**dense vertical bar**). The last 50-ms time interval is not diagrammed. The 40- and 25-μV levels of voltage are indicated, the duration of amplitudes less than 25 μV (16 ms) and less than 40 μV (27 ms) was measured. Fc = frequency of the high-pass filter; NML = normal; T− = true-negative; V(40) and V(50) = 40 and 50 ms of ventricular activation, respectively.

Results

A normal ECG, X, Y and Z leads and a vectormagnitude record are shown in Figures 1A and B from a 21-year-old athlete. The 12-lead standard ECG is normal. Note the relatively sharp decay after the intrinsicoid deflection and the relative lack of QRS notching in the X, Y, and Z leads; also note the very rapid decline toward the terminal end of the QRS in the vectormagnitude record. The last 40 ms of the vectormagnitude recording reveals RMS voltage values of 85 and 42 μV at both HPF frequencies, values well within the normal range. Voltage during the last 40 ms of the QRS recorded with the 25 Hz HPF was considered normal if it was at least 25 μV RMS. Using the 50 Hz HPF, voltage of at least 18 μV RMS was considered normal. Figure 2 is an example of a false-positive result from a normal 29-year-old soccer player whose RMS voltage during the last 40 ms was 22.33 and 16.01 μV, respectively. A 22-year-old male athlete had the lowest voltage in the group during the 40 ms at 25 Hz—12.69 μV RMS. As was the case with all normal subjects, the standard direct writer ECGs were normal in all 3 false-positive patients with QRS duration not in excess of 100 ms. The amplified and filtered vectormagnitude records exceeded 100 ms in 4 subjects in the normal group, 2 of whom had late potentials. Specifically, none revealed intraventricular conduction defects and none had an rSr' pattern in lead V_1.

Using the 25 Hz HPF, the correlation in the group of 50 normal subjects between total QRS duration and the duration of terminal potentials less than 40 μV was poor ($r = 0.362$), as was the correlation with terminal potentials less than 25 uV ($r = 0.453$). The correlation did not improve with 50 Hz HPF.

We also examined the correlation between total QRS duration in the normal subjects and the RMS voltage during the last 40 and 50 ms at 50 Hz. A negative correlation resulted of 0.569 and 0.480, respectively. However, when the correlation was tested between QRS duration and terminal voltage using the 25 Hz HPF as indicated in Figure 3, the negative correlation was somewhat higher during both the last 40 ms ($r = -0.678$) and during the last 50 ms ($r = -0.684$).

For purposes of classification we termed as true-negative any normal subject who had 25 μV or greater in the last 40 ms of the QRS using the 25 Hz HPF. Forty-seven of 50 subjects met this criterion. Three normal subjects failed to meet this criterion and demonstrated late potentials. No other distinguishing fea-

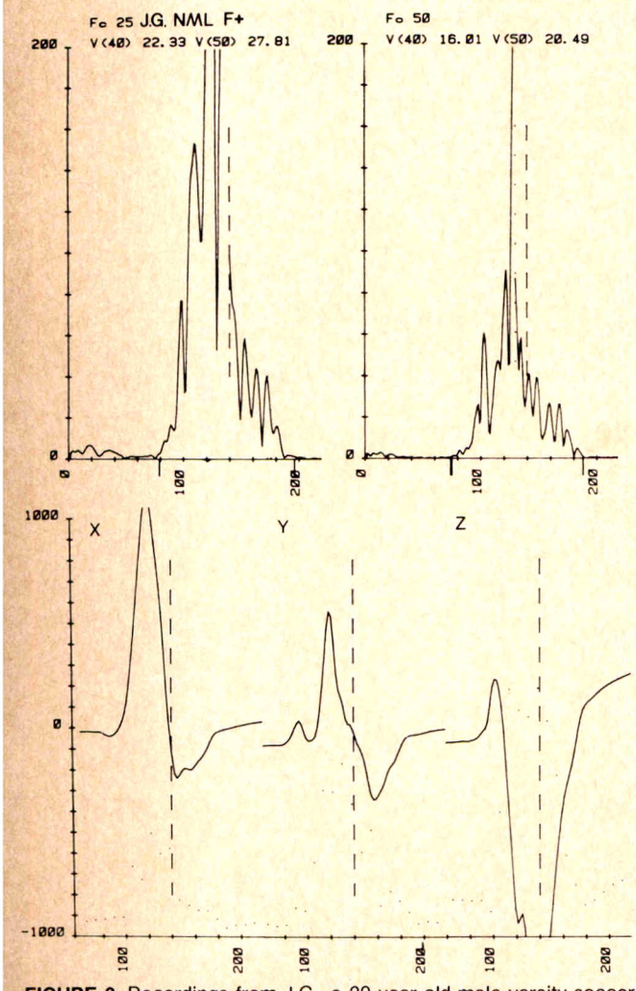


FIGURE 2. Recordings from J.G., a 29-year-old male varsity soccer player, whose voltage during the last 40 ms of the QRS was 22.33 μV root-mean-square with 25 Hz high-pass filter and 16.01 μV root-mean-square with 50 Hz high-pass filter. Contrast the sharp decline in the vectormagnitude record in Figure 1 with the more prolonged lower amplitude higher frequencies in this figure. Further, note the slight increase in mid-QRS notching and slurring visible in the X, Y and Z leads in this illustration, which is less impressive in Figure 1. While the standard 12-lead electrocardiogram did not reveal a QRS greater than 100 ms, the pattern was not that of an intraventricular conduction defect, nor did V_1 show an rSr' pattern, although a relatively prominent S wave in X is noted. F+ = false-positive; other abbreviations as in Figure 1.

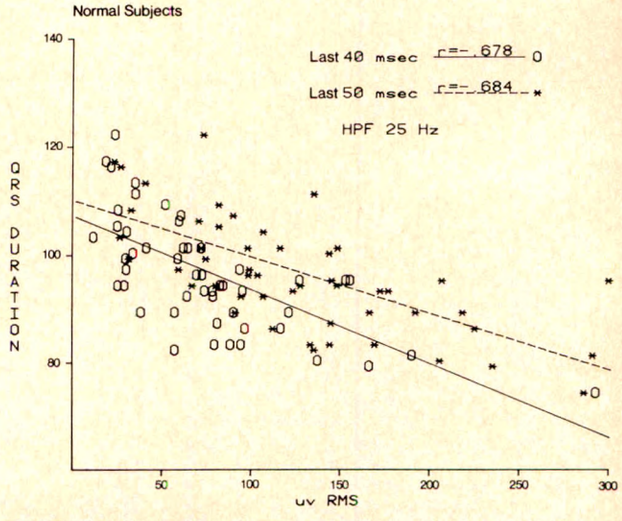


FIGURE 3. With the high-pass filter (HPF) specification at 25 Hz, negative correlation within the normal subject group between QRS duration and the root-mean-square (RMS) of the voltage during the last 40 (**solid regression line** $r = -0.678$) and the last 50 ms (**dashed regression line** $r = -0.684$).

TABLE I Late Potentials in Normal Subjects and in Patients with Ventricular Tachycardia Unrelated to Infarction*

	25 Hz HPF		
	Normal Subjects	VT Patients	p
ms QRS	96.86 ± 1.49	118.36 ± 10.16	NS
μV last 40 ms	76.15 ± 7.31	46.26 ± 9.30	<0.025
μV last 50 ms	126.93 ± 9.61	72.22 ± 13.61	<0.01
ms term. pot. <40 μV	20.80 ± 1.59	33.72 ± 4.87	<0.05
ms term. pot. <25 μV	14.86 ± 1.04	19.27 ± 2.90	NS

* Using the 25 Hz high-pass filter, this table shows results of group comparisons using the 5 measured parameters characterizing late potentials. All values are expressed as mean ± standard error of the mean. Significant differences were established between the normal subjects and the subset with ventricular tachycardia when voltage during the last 40 and 50 ms was considered and when the duration of terminal potentials shorter than 40 μV was considered.

HPF = high-pass filter; NS = not significant; term. pot = terminal potential; VT = ventricular tachycardia.

tures were identified, either clinically or analytically in these subjects. Thus, 94% true-negative and only 6% false-positive responses were seen.

An example of a true-positive response from the VT group is from a patient with hypertensive etiologic factors who demonstrated low voltages of 13.36 μV RMS and 9.11 μV RMS at 40 and 50 Hz, respectively (Fig. 4). A false-negative record from a patient with mitral valve prolapse is illustrated in Figures 5A and B. This patient had occasional sustained VT as well as recurrent nonsustained VT. The coronary arteriogram was normal. Note the sharp decay of the vectormagnitude record with a normal terminal voltage of 85.9 μV and 34.48 μV RMS with 25 and 50 Hz HPF, respectively.

Thus, in the VT group, 5 of 11 patients (or only about 45%) met the true-positive criterion: voltage during the last 40 ms of QRS was under 25 μV RMS (although a sixth patient demonstrated only 25.71 μV RMS). Both patients with standard QRS durations in excess of 120 ms also had low-amplitude late potentials.

Table I lists the comparison of group mean ± standard error of the mean of the 5 parameters measured in the normal group and in the VT group. Unlike other comparative experiences, the total duration of QRS in the normal group and in the VT group did not show statistically significant differences; however, the trend toward a difference is obvious. Although the means are quite different, the reason for lack of significance appears to be a wide standard deviation among the patients with VT. A significant group difference was demonstrated in the voltage during the last 40 and 50 ms and in the duration of terminal potentials using the 25 Hz HPF. Using the 50 Hz HPF, significant differences were shown for the voltage during the last 40 and 50 ms, but not in the other 3 parameters measured (Table II).

Although it was meaningful to make group comparisons, for a diagnostic test to be clinically useful, it should accurately specify a person as belonging to 1 or another diagnostic category. In this light, the overall predictive accuracy of late potentials was 85% using the

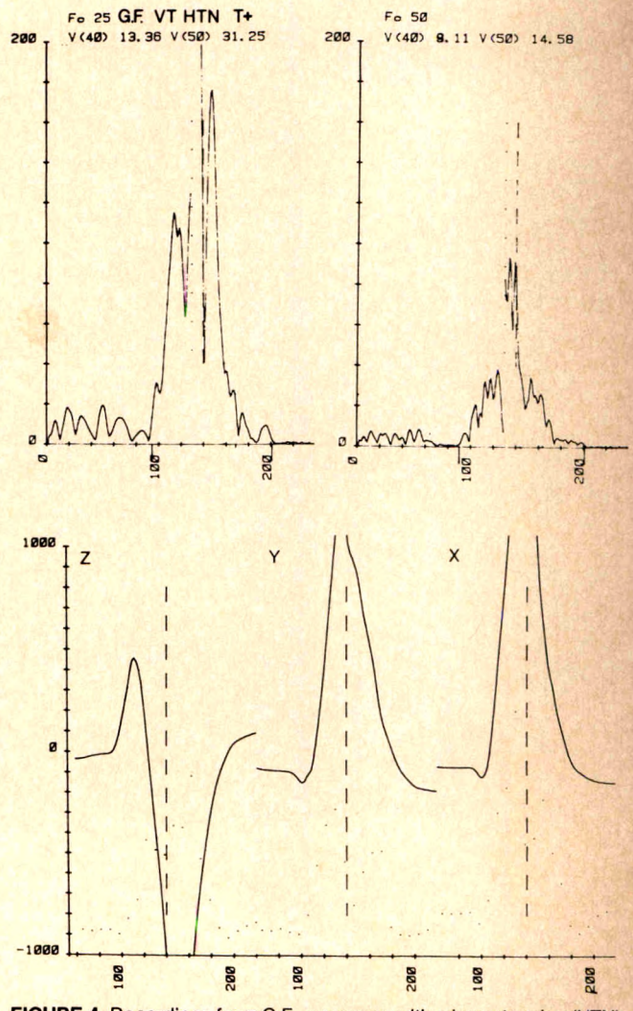


FIGURE 4. Recordings from G.F., a woman with a hypertension (HTN) as a cause of heart disease, who had repeated runs of ventricular tachycardia (VT) and who is representative of our true-positive patients with low-amplitude late potentials of 13.36 and 9.11 μV root-mean-square with 25 and 50 Hz high-pass filter, respectively. Note the trailing out of the low-amplitude tail during the terminal portion of ventricular activation. T+ = true-positive; other abbreviations as in Figure 1.

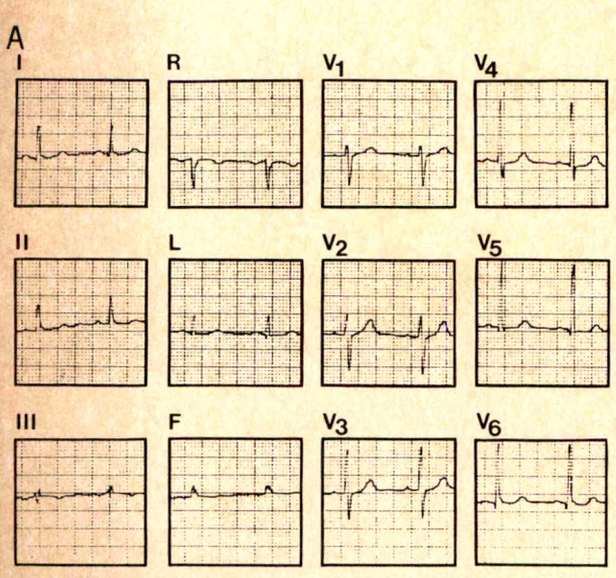
single 25 μV criterion as mentioned (i.e., voltage at least 25 μV for normal subjects and less than 25 μV for patients with VT using the 25 Hz HPF). However, this criterion reflects the good performance in the larger normal group, rather than an equally high positive predictive accuracy.

Using all 5 parameters tested, we sought single values that would better separate the normal subject from the patient with VT. Table III demonstrates that when the 50 Hz HPF was used, 75% of the patients with VT had a potential less than 25 μV RMS for a duration of at least 26 ms, whereas 84% of the normal subjects had a terminal potential less than 25 μV RMS for durations uniformly less than 26 ms. Computer searches at 1-ms intervals up and down the scale from 26 ms resulted in improvement in individual recognition in 1 category, but inevitably a more than equivalent loss in recognition ability in the other category. With use of the 25 Hz HPF, performance of single-point separation of patients with nonischemic, nonsustained VT from normal subsets was less effective.

Disappointed that we were not seeing the degree of late potential discrimination previously encountered when patients with VT secondary to coronary artery disease and MI were studied, we turned our attention to looking at the heart size in this group of patients with VT from multiple, noninfarction causes. An interesting relation emerged (Table IV). The patients with VT, who also had cardiothoracic ratios in excess of 0.5 in the 72-inch upright posteroanterior roentgenogram of the chest, uniformly revealed the lower terminal voltage. Conversely, patients with VT with normal-sized hearts had the higher terminal voltages. There was a 34.2 μV RMS jump that occurred between the patient with the highest voltage with cardiomegaly and the patient with the lowest voltage with a normal cardiac silhouette. This latter patient had the largest heart (meeting the radiographic criterion for normal) and barely met the terminal potential magnitude criterion of normal. The etiology was cardiomyopathic. Because alcohol consumption was not a consideration, and because he had a severe viral infection before an acute onset of ventricular rhythm, the cause was presumed to be viral. Cultures and titers were not obtained. The left ventricular ejection fraction derived from catheterization data was 28% and the coronary arteries were normal. The standard ECG did not reveal left ventricular enlargement.

Discussion

Recordings with the 50 Hz HPF were found to be only slightly more reproducible on successive days than they were with the 25 Hz HPF. The optimal single point of



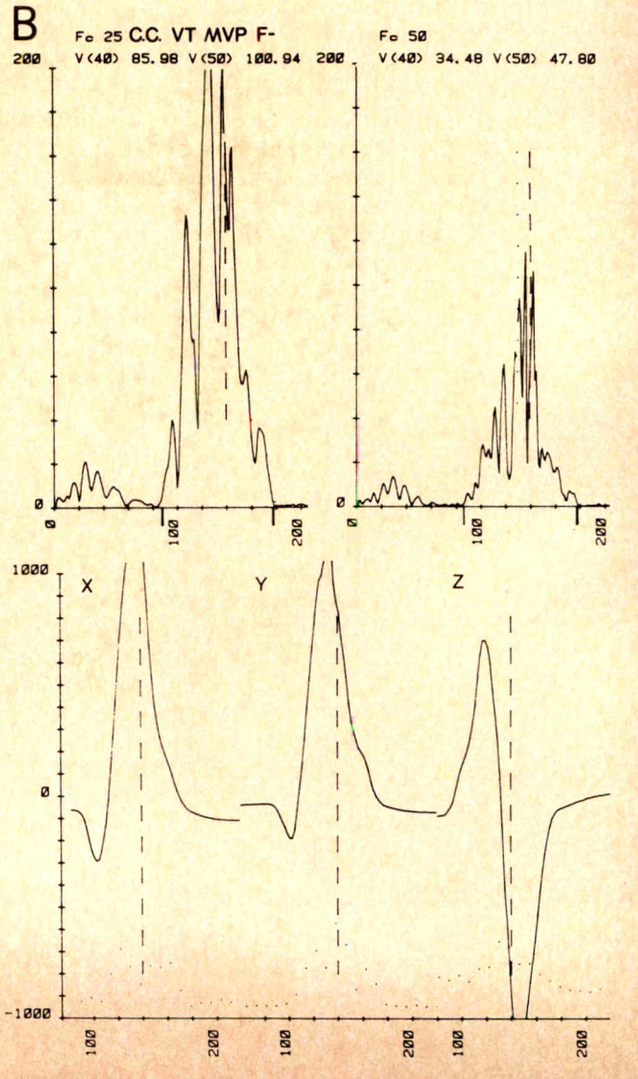


FIGURE 5. A, electrocardiogram, and **B,** X, Y and Z leads and vector-magnitude record from C.C., a patient representative of the false-negatives with sustained ventricular tachycardia and a diagnosis of mitral valve prolapse (MVP). Coronary arteriography revealed no significant coronary artery disease. Note the normal routine electrocardiogram and the very sharp decline of QRS with the terminal voltage well above the 25 μV RMS level which was 85.9 μV with the 25 Hz high-pass filter, and 34.48 μV RMS with the 50 Hz high-pass filter. A relatively normal set of orthogonal leads X, Y and Z, as well as the filtered leads, was recorded. F— = false-positive; other abbreviations as in Figure 1.

TABLE II Late Potentials in Normal Subjects and in Patients with Ventricular Tachycardia Unrelated to Infarction*

	50 Hz HPF		
	Normal Subjects	VT Patients	p
ms QRS	95.38 ± 1.53	110.0 ± 11.03	NS
μV last 40 ms	40.77 ± 5.86	20.10 ± 4.94	<0.025
μV last 50 ms	60.08 ± 6.71	27.23 ± 5.65	<0.005
ms term. pot. <40 μV	28.43 ± 1.88	50.29 ± 14.36	NS
ms term. pot. <25 μV	22.08 ± 1.66	35.43 ± 8.25	NS

* Group comparisons using the 5 parameters measured from data recorded with the 50 Hz high-pass filter (HPF). Groups are statistically different when voltage during the last 40 or 50 ms of QRS were considered.

Abbreviations as in Table I.

TABLE III Late Potentials in Normal Subjects and in Patients with Ventricular Tachycardia Unrelated to Infarction*

	Correct Classification 50Hz HPF	
	Patients with Nonsustained VT (%)	Normal Subjects (%)
Last 40 ms	57 <20 μV	86 ≥20 μV
Last 50 ms	57 <30 μV	94 ≥30 μV
Last 40 ms	57 <15 μV	94 ≥15 μV
Last 50 ms	57 <25 μV	94 ≥25 μV
QRS duration	57 >110 ms	100 ≤110 ms
Duration <40 μV term. pot.	72 ≥30 ms	66 <30 ms
Duration <40 μV term. pot.	57 ≥37 ms	90 <37 ms
Duration <25 μV term. pot.	75 ≥26 ms	84 <26 ms

* Using the 5 parameters tested, single values were sought that would separate the normal subset from the patient with ventricular tachycardia. The 50 Hz high-pass filter was slightly more effective than the 25 Hz high-pass filter in achieving the best group separation. The most effective point of separation was the 26-ms duration of terminal potentials shorter than 25 μV. In the normal subjects, 84% had terminal potentials shorter than 25 μV that lasted under 26 ms, whereas in 75% of patients with VT the duration was at least 26 ms. See text.

Abbreviation as in Table I.

discrimination between the normal subject and the patient with nonsustained VT was found with the 50 Hz HPF (Table III). Group differences were seen with both HPF frequencies, but the most significant group difference (i.e., the voltage during the last 50 ms) was with the 50 Hz filter (Table II). In comparing effectiveness of discrimination of 2 different filter frequencies, 1 consideration should be recognized. For example, if frequency content between 25 and 50 Hz is abundantly represented at the end of QRS, the duration of the recording may be slightly shorter with the 50 than with the 25 Hz HPF. In comparing the results of 1 study with another, filter frequencies that vary between studies more widely than those represented in this study could become a major consideration.

A ready explanation was not forthcoming for the 3 normal subjects who revealed late potentials less than 25 μV RMS during the last 40 ms of the QRS. Whereas the hearts of these 3 subjects (all of whom are varsity soccer players) were at the upper limits of normal, none exceeded a cardiac thoracic ratio of 0.5. One subject was black, 1 was white, and 1 was Hispanic of South American Indian extraction.

We thought it logical to attempt a correlation between the total QRS duration and the duration of late potentials. We reasoned that because total QRS duration tends to increase in patients after MI, often with some degree of conduction delay in the low-amplitude terminal QRS, it might also relate to a parallel spectrum of low-amplitude terminal potential durations in normal subjects. This was not found to be the case as evidenced by the low r values. Although the ability of terminal potential amplitude or duration to distinguish the abnormal from the normal group was quite good, the ability to correctly specify persons within the VT group was much less impressive. All subjects had very symptomatic, recurrent episodes of nonsustained VT, although 1 also had an occasional episode of sustained VT, lasting longer than 30 seconds. The fact that only 2 subjects in the present study had a history of MI (and these events occurred in the remote past) suggests that this group of subjects with VT is basically very different from groups in earlier studies in which ischemic disease was implicit and the tachycardias were sustained.

The precise ultrastructural and functional relations of surface recorded late potentials, notches and slurs, and the fragmented epicardial electrogram remain unclear and is a rich field for investigation. Perhaps the most significant observation in this study is that, for whatever reason, the lower terminal voltage was clearly concentrated in patients with larger hearts. This observation may bear a relation to an earlier finding, that even in the absence of infarction, ventricular enlargement from any cause is also associated with an alteration in ventricular activation manifested by an increase in QRS notching.[7,8]

Correspondence between fragmented electrograms recorded directly from the heart and late potentials

TABLE IV Relations of Heart Size to Late Potentials in Patients with Ventricular Tachycardia

VT	↑ Heart CXR	Last 40 ms μV RMS
Hypertension	+	13.36
CAD	+	17.77
CAD	+	21.14
CAD	+	21.92
MVP	+	24.30
Cardiomyopathy	+	25.71
Mellaril	0	59.93
CAD	0	64.34
AVD	0	81.39
MVP	0	85.98
Cardiomyopathy	0	93.02
	25 Hz HPF	

The most likely cause of heart disease is listed for each patient. Two of the patients with coronary artery disease were so diagnosed because of a history of remote myocardial infarction. One other had greater than 50% diameter encroachment of a single coronary artery, and a fourth had minimal plaque formation only. Note the 34.22-μV difference between the patient with an enlarged heart with the highest voltage (25.71) and the patient with a normal-sized heart with the lowest (59.93). AVD = aortic valve disease; CAD = coronary artery disease; CXR = chest x-ray; HPF = high-pass filter; HTN = hypertension; MVP = mitral valve prolapse; RMS = root-mean-square; VT = ventricular tachycardia; + = yes; 0 = no.

recorded from the body surface has been pointed out by Simson et al.[9] Gardner et al[10] explored the nonuniform anisotropic border zone in the canine heart and pointed out that transmembrane action potentials may be normal at this time, though conduction remains very slow, presumably because the junctions between surviving myocardial fibers in the healed infarcts are very sparse. With premature stimulation, conduction block readily occurs, and this may cause reentry. These investigators emphasize that the structure of infarcts may be as important as the characteristics of the transmembrane potentials of the surviving muscle fibers in causing reentrant excitation. Along the same line, also in canine infarcts, evidence was presented that slow conduction alone does not cause fragmented activity. The appearance of fractionated electrograms in 2-week-old infarction seems to coincide with the increase in connective tissue in the epicardial border zone, which separates the myocardial fibers and eventually distorts the orientation. These investigators believe that the individual components of the fragmented electrograms most likely represent asynchronous electrical activity in separate bundles of surviving muscle under the recording electrode. They conclude that the anatomic substrate for reentry is present where fragmented electrograms can be recorded, because these electrograms indicate slow, inhomogeneous conduction. However, they emphasize that fragmented electrograms are probably found wherever myocardial fibers are separated by connective tissue, whether or not reentry occurs in the region.[10]

Can these very fundamental insights be applied to explain why, in this study of nonischemic patients with VT, surface recorded terminal potentials of low amplitude appeared only when cardiomegaly was present, but were not present in subjects with normal-sized hearts? A possibility worth considering is that, because fragmented electrograms are found when myocardial fibers are separated by connective tissue, in the patient with a noninfarcted heart, a critical degree of connective tissue separation must occur as a result of gradual cardiac enlargement, before late potentials can be recorded by surface techniques, even with the use of signal averaging. Conversely, after MI in the patient with ischemic heart disease, such fibrotic separation may occur well before marked enlargement occurs.

In conclusion, much basic work must be done to explain the relations of the various markers of alteration of the process of ventricular excitation.

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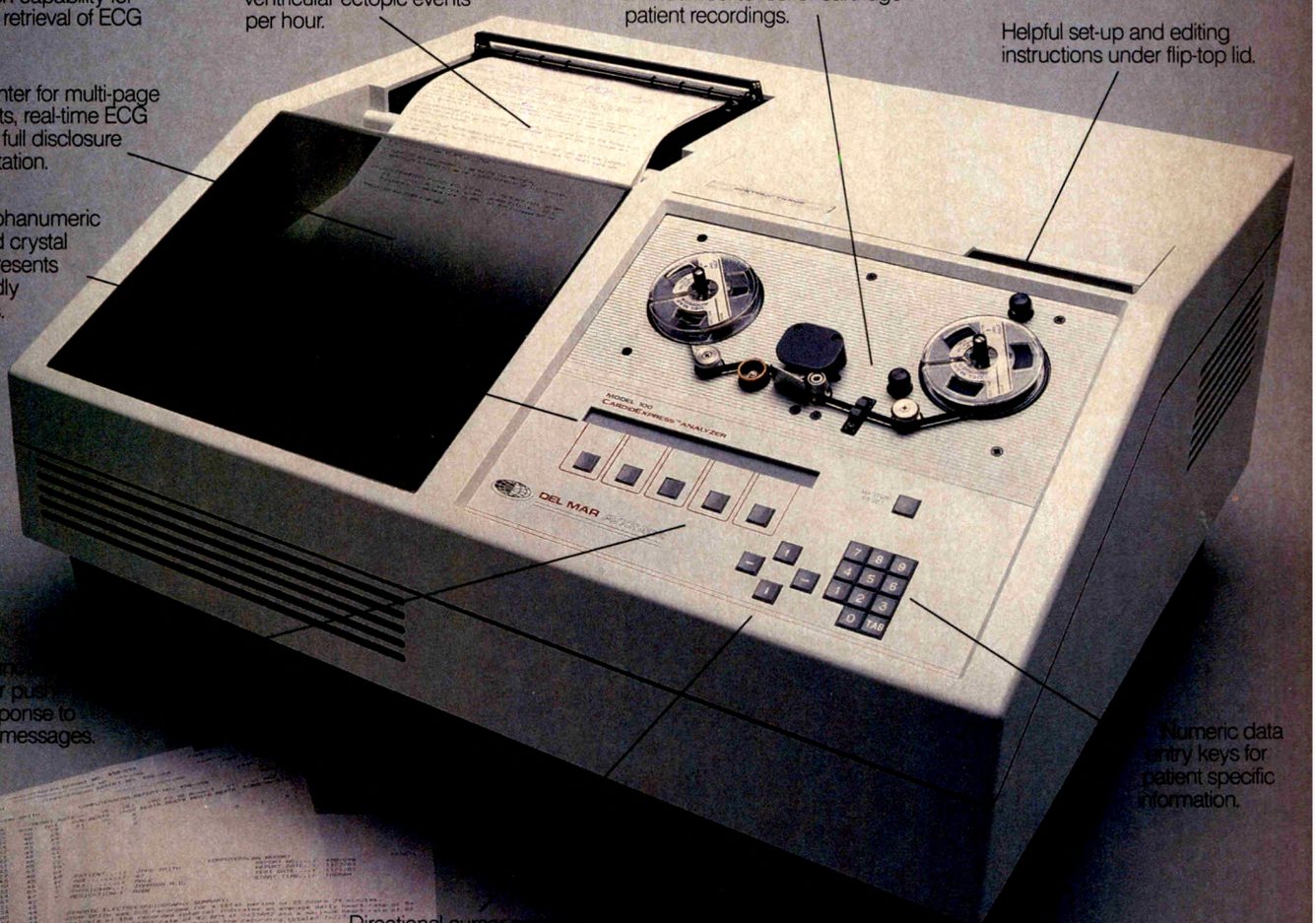

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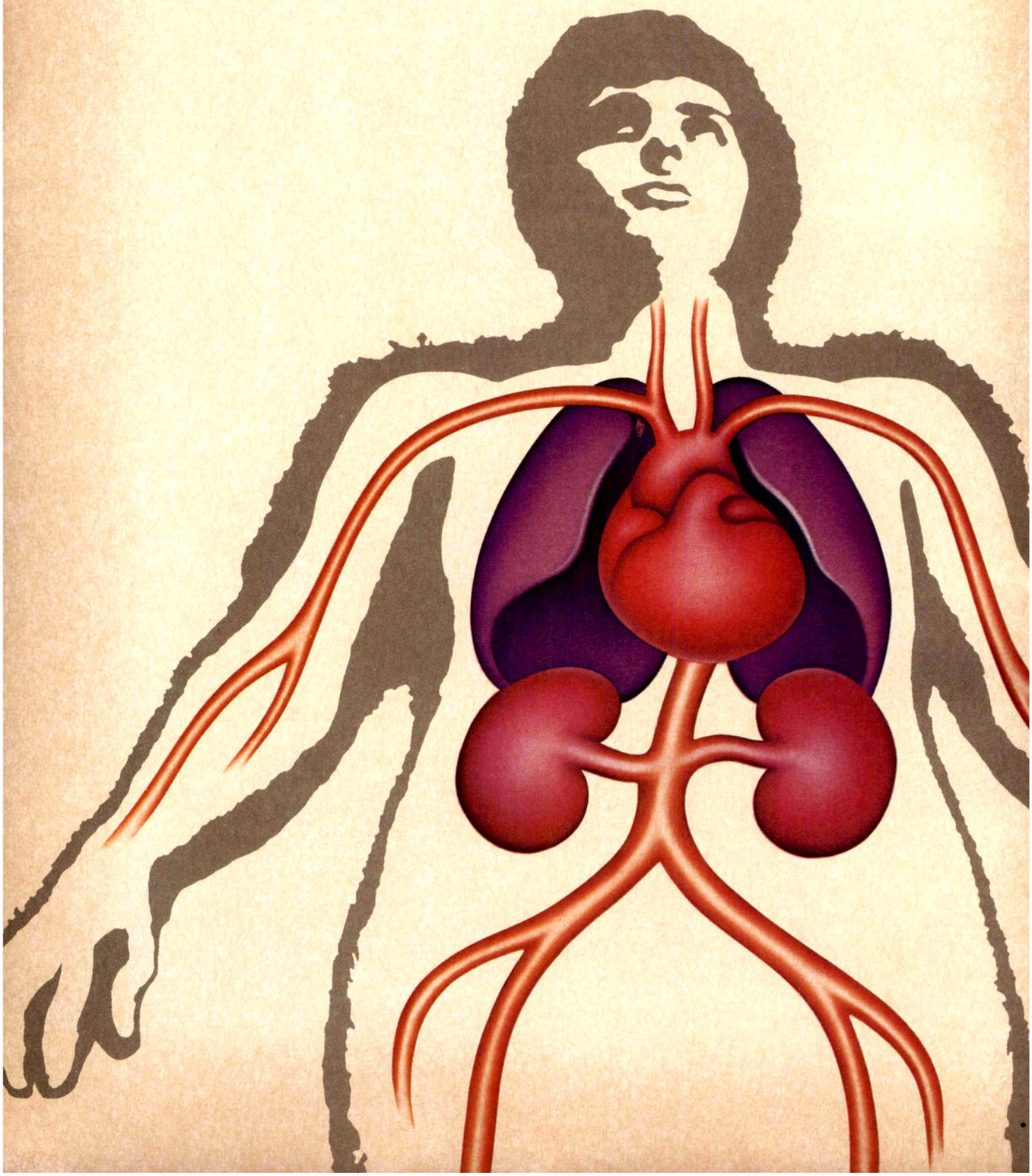

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Normodyne® (labetalol HCl) is a unique single-entity agent. It acts as a beta blocker as well as an alpha$_1$ vasodilator, offering the advantages of both while avoiding many of the disadvantages. Beyond beta blockers, it also acts as a vasodilator to lower blood pressure. Beyond vasodilators, it acts as a beta blocker to blunt excessive cardiac response to exercise in hypertensives.

- Unsurpassed efficacy in mild to moderate hypertension.
- Useful in a wide diversity of patient types.
- Favorable side-effects profile.
- A demonstrated safety profile.
- Well documented in hundreds of clinical studies.
- Millions of patients treated worldwide.
- Compliance-enhancing b.i.d. dosage.

The unique single-entity blocker/dilator

NORMODYNE®

Tablets (labetalol HCl)

Please see brief summary of prescribing information at the end of this advertisement.

Differences that direct patient benefits

Efficacy

A comprehensive review of worldwide literature has shown the efficacy of Normodyne® (labetalol HCl) to be unsurpassed in mild to moderate hypertension. Comparative drugs in these studies included beta blockers, alpha adrenergic blocking agents and centrally acting antihypertensives.

- Effective alone or in combination with a diuretic.
- Prompt onset of action, usually within two hours.[1,2]
- Easily titrated to achieve desired effect.
- No tolerance development as shown in clinical studies up to one year.

Convenient b.i.d. dosage.

Initiate therapy with one-half (1/2) scored 200 mg tablet b.i.d. Instruct patient to continue this regimen until the first follow-up visit, which should occur in three to seven days. Patient should be told to phone about any problems or other concerns.

Versatility

Normodyne® (labetalol HCl) may be used in a wide diversity of patients, including:

The elderly

In a year-long study,[3] Normodyne lowered blood pressure smoothly and safely in patients with a mean age of 66 without causing problems of frequent concern when treating hypertension in the elderly. (Some patients may be maintained at lower doses.)

Active hypertensives Normodyne does not impede cardiac response to sports or strenuous activity. It does not adversely affect blood flow to vital organs and produces a low incidence of fatigue and drowsiness.

Black patients Normodyne has been shown to be effective in reducing and controlling hypertension in black patients.[4]

translate into... and fewer limitations.

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Side effects

Normodyne® (labetalol HCl) has a favorable side-effects profile.*

Unlike propranolol, a conventional beta blocker, Normodyne produces a low incidence of

- fatigue (5%)
- bradycardia (none reported in controlled clinical trials)
- cold extremities (none reported in controlled clinical trials)

Unlike vasodilators, a low incidence of

- orthostatic hypotension (1%)
- tachycardia (none reported in controlled clinical trials)
- headaches (2%)

Most adverse effects are mild, transient and occur early in the course of treatment. In 3-to-4 month controlled clinical trials, the most common side effects noted in treating mild to moderate hypertension with Normodyne include dizziness (11%), nausea (6%), and fatigue (5%). Dyspepsia (3%) and nasal stuffiness (3%) occurred to a lesser degree.

Safety

Normodyne® (labetalol HCl) has a demonstrated safety profile.

Co-existing COPD.[5,6] Patients with non-allergic bronchospasm should, in general, not receive beta blockers. Normodyne may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents.†

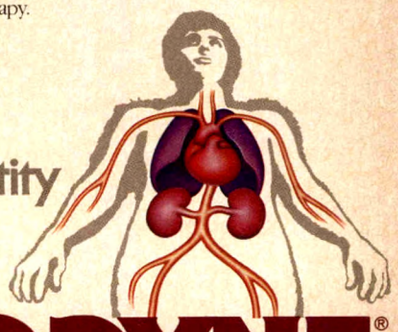
Co-existing controlled CHF.[7] Although beta blockers as a class should be avoided in *overt* congestive heart failure, Normodyne can be used, if necessary, in patients with a history of heart failure who are well compensated.

Co-existing CAD. In patients with hypertension and coronary artery disease, Normodyne reduced blood pressure, maintained cardiac output and blunted excessive response to exercise.[8-11]††

Vital organs & serum lipids. Normodyne did not adversely affect perfusion of brain, heart, lungs and kidneys. Nor was renal function in renally impaired patients or in those with normal kidney function adversely affected.[12] Normodyne also did not adversely affect serum levels of HDL-cholesterol, total cholesterol, or triglycerides.

† It is prudent, if Normodyne is used in these patients, to use the smallest effective dose so that inhibition of endogenous or exogenous beta-agonists is minimized.

†† Patients should be advised to consult their physicians before discontinuing therapy.



The unique single-entity blocker/dilator for hypertension

NORMODYNE®

Tablets (labetalol HCl)

Please see brief summary of prescribing information and references at the end of this advertisement.

NORMODYNE®
brand of labetalol hydrochloride
Tablets
BRIEF SUMMARY

INDICATIONS AND USAGE
NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS
NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia. (See **WARNINGS.**)

WARNINGS
Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS
General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately, should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients
As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests
As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions
In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions
The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C
Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery
Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers
Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effect was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Syncope. *Central and Peripheral Nervous Systems* Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment. *Collagen Disorders* Systemic lupus erythematosus; positive antinuclear factor (ANF). *Eyes* Dry eyes. *Immunological System* Antimitochondrial antibodies. *Liver and Biliary System* Cholestasis with or without jaundice. *Musculo-Skeletal System* Muscle cramps; toxic myopathy. *Respiratory System* Bronchospasm. *Skin and Appendages* Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia. *Urinary System* Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block.
See **CONTRAINDICATIONS.**

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE
Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a beta$_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

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Schering Corporation
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Ventricular Arrhythmia Induced by Programmed Ventricular Stimulation After Acute Myocardial Infarction

PIETRO SANTARELLI, MD, FULVIO BELLOCCI, MD, FRANCESCO LOPERFIDO, MD, MARIO MAZZARI, MD, ROCCO MONGIARDO, MD, ANNIBALE S. MONTENERO, MD, UGO MANZOLI, MD, and PABLO DENES, MD

The prevalence, characteristics and clinical significance of ventricular electrical instability with programmed ventricular stimulation was studied in 50 hemodynamically stable patients 17 to 40 days after acute myocardial infarction (AMI) using double extrastimuli at 2- and 10-mA intensity and from 2 right ventricular sites. Ventricular electrical instability was defined as induction of 10 or more consecutive intraventricular reentrant beats. Of 50 patients, 23 (46%) had ventricular electrical instability (10 of these had sustained ventricular tachycardia [VT] induced). No significant differences were observed between patients with and without ventricular electrical instability with respect to age, site of AMI, coronary prognostic index, maximal level of CK, number of narrowed coronary arteries and presence of severe wall motion abnormalites. During a mean follow-up of 11.2 months no patient died suddenly. During repeated Holter recordings patients with ventricular electrical instability had a higher incidence of nonsustained VT than did patients without ventricular electrical instability.

(Am J Cardiol 1985;55:391–394)

Previous studies[1–3] have presented evidence that after acute myocardial infarction (AMI) programmed ventricular stimulation is a sensitive and specific method for identification of patients at high risk of having ventricular tachycardia (VT) or sudden death. We report the results of a prospective study of programmed ventricular stimulation in the late hospital phase of AMI. Specifically we studied (1) the prevalence and the characteristics of the induced ventricular arrhythmias, (2) the correlation between the induced ventricular arrhythmias and the clinical, Holter monitoring and angiographic findings, and (3) the results of follow-up.

Methods

Patients: One hundred thirty-eight patients were admitted to the coronary care unit with documented AMI from October 1982 to October 1983. Nineteen of these 138 patients died before discharge. Of the remaining 119 patients, 50 (49 men and 1 woman, mean age [± standard deviation] 53 ± 9 years), were entered in the study 25 ± 5 days (range 17 to 40) after AMI. Criteria for inclusion in the study were: (1) documented (clinical history, serial electrocardiogram and serum enzyme changes) and recent (less than 6 weeks) AMI; (2) absence of intractable congestive heart failure or cardiogenic shock; (3) written informed consent; and (4) absence of significant (more than 50% narrowing) left main coronary artery narrowing and rheumatic valvular heart disease.

The study protocol consisted of: (1) coronary angiography and left ventriculography, (2) electrophysiologic study, including programmed ventricular stimulation at least 30 minutes after coronary angiography, and (3) 24-hour Holter monitoring the day before the invasive studies.

Ambulatory electrocardiographic monitoring: Twenty-four-hour Holter monitoring was performed 24 to 36 hours before cardiac catheterization and after all antiarrhythmic drugs had been withdrawn for a period of 5 half-lives. The recording system (Hittman Comp-Act IV) allowed simultaneous recording of 2 electrocardiographic leads (V_1 and V_5). An audiovisual scanning technique was used to review tape records. The interpretation was done by physicians who reviewed direct printouts of each grade of premature ventricular beats. The frequency, configuration and timing of spontaneous premature ventricular beats were classified according to the Lown grading system.[4] During follow-up, the 24-hour Holter monitoring was repeated.

From the Section of Cardiology, Catholic University, School of Medicine, Rome, Italy and Rush-Presbyterian St. Luke's Medical Center, Chicago, Illinois. Manuscript received July 6, 1984; revised manuscript received September 30, 1984, accepted September 24, 1984.

Address for reprints: Pietro Santarelli, MD, Istituto di Cardiologia, Policlinico A. Gemelli, Largo A. Gemelli 8, Rome, Italy 00168.

TABLE I Clinical Characteristics

	All	VEI	No VEI	p
No. of pts	50	23	27	
Mean age (yrs) (± SD)	53 ± 9	53 ± 10	53 ± 9	NS
Men/women	49/1	22/1	27/0	NS
Site of MI				
Anterior	17	6 (26)	11 (40)	NS
Inferior	30	16 (69)	24 (51)	NS
Nontransmural	3	1 (4)	2 (7)	NS
Previous MI	2	1	1	NS
Killip I	32	16	16	NS
Killip II	18	7	11	NS
Maximal CK (IU/liter)	1,304 ± 845	1,083 ± 14	1,220 ± 567	NS
Spontaneous VT/VF (CCU)	4	2 (8)	2 (7)	NS
Spontaneous VT (late)	3	3 (23)	0 (0)	NS
Holter findings (Lown class)				
<3	26	7 (31)	19 (71)	<0.01
≥3	24	16 (69)	8 (29)	
4B	6	5 (21)	1 (3)	NS

CCU = coronary care unit; CK = creatine kinase; MI = myocardial infarction; NS = not significant; SD = standard deviation; VEI = ventricular electrical instability; VF = ventricular fibrillation; VT = ventricular tachycardia.

Cardiac catheterization: Sixty patients underwent cardiac catheterization using a femoral approach. A maximum of 8 ml of 1% xylocaine was used as local anesthetic. Two quadripolar catheters (No. 6Fr or 7Fr) were introduced into the femoral vein. Left-sided cardiac catherization was performed using the Judkins technique and included single-plane left ventriculography in the right anterior oblique position, and coronary angiography. Narrowing of the left main coronary artery less than 50% in diameter or severe angina during catheterization led to termination of the procedure.

Electrophysiologic study: Of the 119 patients who entered the study, 52 refused consent and 7 had severe congestive heart failure or cardiogenic shock, or both. Sixty patients underwent cardiac catheterization, and 50 of these had electrophysiologic study at least 30 minutes after angiography. Ten patients were excluded: 3 with left main disease, 4 with prolonged chest pain during angiography and 3 with valvular heart disease.

The right coronary catheter was positioned in the descending aorta below the renal arteries to monitor blood pressure. One quadripolar catheter (interelectrode distance of 1 cm) was positioned across the tricuspid valve to record the His bundle electrogram and another quadripolar catheter (interelectrode distance of 1 cm) was used to pace and record from the high right atrium and the right ventricle. Surface electrocardiographic leads I, III and V_1 together with 2 intracardiac electrograms (filtered at 50 to 300 Hz) were recorded on magnetic tape and reproduced on a multichannel recorder (Hewlett-Packard 1308A) at a paper speed of 100 mm/s. Pacing was performed using a Medtronic 5325 programmable stimulator delivering rectangular pulses 2 ms in duration. No patient was taking antiarrhythmic or β-blocking drugs at the time of the study.

Programmed ventricular stimulation was performed in a preestablished sequence to an end point of 10 or more induced consecutive intraventricular reentrant beats. This response was considered to represent ventricular electrical instablity. The programmed ventricular stimulation sequence was: ventricular pacing at 2 cycle lengths (S_1S_1—600 ms and 462 ms) with single extrastimulus (S_2) from the right ventricular apex at 2 mA; ventricular pacing at the same cycle lengths with double extrastimuli (S_2S_3) from the right ventricular apex at 2 mA. If the end point was not reached, sequences 1 and 2 were repeated at a stimulus intensity of 10 mA. Then the catheter was moved to the right ventricular outflow and sequences 1 and 2 repeated at 2 mA and 10 mA. Sustained VT was defined as VT that caused hemodynamic compromise which required pacing or cardioversion for immediate termination or if stable lasting for at least 30 seconds. Nonsustained VT was defined as VT that lasted less than 30 seconds. No complications related to the study were observed.

Follow-up: All patients were followed up at regular intervals up to 16 months (338 ± 99 days, range 128 to 483) by telephone or in the clinic. The results of programmed ventricular stimulation did not influence subsequent management except in 3 patients who had both spontaneous and induced sustained VT. When clinically indicated, complex ventricular arrhythmias were treated with amiodarone.

Statistical analysis: Statistical analysis was performed by using χ^2 and the Student t test for unpaired data. All values given in the text represent mean ± standard deviation of the mean. Differences were considered significant when $p < 0.05$.

Results

Clinical characteristics: The clinical characteristics of the study group are presented in Table I. Seventeen patients had an anterior, 30 an inferior and 3 a nontransmural AMI. Two patients had prior AMI. Eighteen patients were in Killip class II on admission and 32 patients in Killip class I. Maximal CK (IU/liter) was 1,304 ± 845. Sustained VT or ventricular fibrillation (VF) occurred in the coronary care unit in 4 patients, while 3 patients presented with sustained VT in the late phase (11, 17 and 18 days after admission). Complex ventricular arrhythmias (Lown class III or higher) were observed in 24 patients and episodes of nonsustained VT (3 or more consecutive premature ventricular beats) were documented in 6 (Table I).

Angiographic findings: One-vessel disease was present in 21 patients, 2-vessel disease in 16 and 3-vessel disease in 12, and 1 patient had no significant coronary artery narrowing. The mean ejection fraction was 0.45 ± 0.10, and 20 patients had an ejection fraction less than 0.40. The mean left ventricular end-diastolic pressure was 14.7 ± 5 mm Hg and more than 20 mm Hg in 9 patients. Severe wall motion abnormalities were observed in 34 patients.

Electrophysiologic findings: Twenty patients had 0 to 4 beats at intraventricular reentry, 7 patients 5 to 9, 5 patients 10 to 20, and 8 patients more than 20. Ten

TABLE II Mode of Induction of Intraventricular Reentrant Beats in the Group with Ventricular Electrical Instability

	RVA		RVO	
	S_1S_2	$S_1S_2S_3$	S_1S_2	$S_1S_2S_3$
2 mA	2	10	0	3
10 mA	0	5	0	3

VEI = ventricular electrical instability; RVA = right ventricular apex; RVO = right ventricular outflow tract.

patients had sustained VT induced. Twenty-three patients (46%) had 10 or more (ventricular electrical instability group) and 27 (54%) had 10 or less beats induced. Of the 23 patients with ventricular electrical instability, 10 had sustained and 13 had nonsustained VT. In the sustained VT group, 7 patients showed monomorphic tachycardia (cycle length 268 ± 72 ms): 5 with left bundle branch block and 2 with right bundle branch block morphology; and 3 patients had polymorphic VT induced (cycle length 186 ± 15 ms). In the nonsustained VT group, 5 patients had monomorphic VT induced (cycle length 212 ± 13 ms): 4 with left bundle branch block and 1 with right bundle branch block morphology; and 8 patients had polymorphic VT induced (cycle 200 ± 35 ms).

The mode of induction of the intraventricular reentry in the 23 patients with ventricular electrical instability is listed in Table II. In 17 patients, intraventricular reentry was induced from the right ventricular apex, using single extrastimulus in 2 and double in 15; intraventricular reentry was induced at 2 mA in 12 and at 10 mA in 5. In 6 patients intraventricular reentry was induced from the right ventricular outflow, using double extrastimuli at 2 mA in 3 and at 10 mA in 3.

Of the 10 episodes of sustained VT, 5 were terminated by short bursts of ventricular pacing and 5 required cardioversion for rapid hemodynamic deterioration.

Comparison between groups with and without ventricular electrical instability: Twenty-three patients (46%) had 10 or more intraventricular reentrant beats induced (ventricular electrical instability group) and 27 (54%) had 10 or less consecutive beats (group without ventricular electrical instability) initiated with programmed ventricular stimulation. No significant differences were observed in age, site of myocardial infarction, maximal CK and occurrence of spontaneous sustained VT or VF (early or late). All 3 patients who had spontaneous sustained VT in the late hospital phase had their clinical VT induced (Table I).

Holter monitoring showed that 16 patients (69%) in the ventricular electrical instability group had Lown class 3 or higher arrhythmia compared with 8 patients (29%) in the group without ventricular electrical instability ($\chi^2 = 6.42$, $p = <0.01$). Five patients (21%) in the group with and 1 (3%) in the group without ventricular electrical instability had nonsustained VT (Lown class 4B) ($\chi^2 = 2.31$, difference not significant [NS]).

No significant differences were found between the group with and the group without ventricular electrical instability with respect to ejection fraction (0.42 ± 0.7 vs 0.47 ± 0.12), prevalence of 1-vessel (43% vs 41%), 2-vessel (35% vs 30%) and 3-vessel disease (22% vs 26%). One patient (3%) in the group without ventricular electrical instability had no angiographic coronary disease. The mean left ventricular end-diastolic pressure was 15 ± 4 mm Hg in the ventricular electrical instability group and 14 ± 5 mm Hg in the group without ventricular electrical instability (NS). Five patients (18%) in the group with and 4 (15%) in the group without ventricular electrical instability had a left ventricular end-diastolic pressure greater than 20 mm Hg (NS). Severe wall motion abnormalities (1 or more akinetic or dyskinetic segments) were found in 18 patients (78%) in the group with in 16 (59%) in the group without ventricular electrical instability (NS).

TABLE III Therapy and Holter Monitoring Data in Patients With and Without Ventricular Electrical Instability During Follow-Up

	VEI (23 pts)	No VEI (27 pts)	p
Amiodarone (275 ± 103 mg/day)	8 (34%)	4 (14%)	NS
β-blocking drugs	4 (17%)	4 (14%)	NS
CABG	2 (8%)	5 (19%)	NS
Lown class >3	13 (76%)	12 (60%)	NS
Lown class 4B	6 (35%)	0 (0%)	<0.01

* Holter monitoring data were available in 17 patients in the group with and 20 patients in the group without ventricular electrical instability.

CABG = coronary artery bypass graft; NS = not significant; VEI = ventricular electrical instability.

Follow-up data: The discharge medications are listed in Table III. No significant treatment differences were observed between the 2 groups (amiodarone 34% vs 14%, β-blocking drugs 17% vs 14%, and coronary artery bypass surgery 8% vs 19%).

Thirty-seven patients had at least one 24-hour Holter recording during follow-up (17 in the group with and 20 in the group without ventricular electrical instability) (Table III). Lown class 3 or higher ventricular arrhythmias were present in 76% of the group with and in 60% of the group without ventricular electrical instability ($\chi^2 = 1.3$, NS). Nonsustained VT was observed in 35% of the patients in the group with and in none of the patients in the group without ventricular electrical instability ($\chi^2 = 8.7$, $p = <0.01$). During a mean follow-up of 11.2 months, 1 patient died from sepsis in the group with ventricular electrical instability, after coronary artery surgery. There were no sudden deaths in either group.

Discussion

We prospectively evaluated the clinical significance of intraventricular reentry induced by programmed ventricular stimulation in 50 consecutive, hemodynamically stable patients, who had survived the acute phase of myocardial infarction. Our major findings were: (1) programmed ventricular stimulation, performed 17 to 40 days (mean 25) after myocardial infarction, showed a high prevalence of ventricular electrical instability (46%) and, (2) ventricular electrical instability

did not correlate with hemodynamic and angiographic data.

Green et al,[1] using a PVS protocol, including a single ventricular extrastimulus during atrial pacing, induced intraventricular reentry (1 or more ventricular premature beats) in 19 (39%) of the 48 patients after AMI. Hamer et al,[2] using a more aggressive protocol (double ventricular extrastimuli at 2 right ventricular sites, and a stimulus intensity of 2 V and 10 V, studied 70 patients 7 to 20 days (mean 11) after AMI. Ventricular electrical instability, defined as more than 5 consecutive premature ventricular beats, was observed in 12 patients (17%). Richards et al,[3] using a similar programmed ventricular stimulation protocol (double ventricular extrastimuli at 2 right ventricular sites, and stimulus intensity of twice diastolic threshold and 20 mA) studied 165 patients 6 to 28 days (mean 10) after AMI. Ventricular electrical instability, defined as induction of VF or VT lasting at least 10 seconds, was found in 38 patients (23%). Marchlinski et al,[5] using single and double ventricular extrastimuli from the right ventricular apex, studied 46 patients 8 to 60 days (mean 22) after AMI. Ventricular electrical instability, defined as sustained VT or nonsustained VT (4 or more beats), was observed in 8 patients (18%). Borggrefe et al,[6] using single and double ventricular extrastimuli during sinus rhythm and several ventricular paced cycle lengths, studied 203 patients up to 60 months after AMI. Ventricular electrical instability, defined as 4 or more ventricular echo beats, was found in 20% of those studied 1 month or less after the infarct.

In our study, using a programmed ventricular stimulation protocol similar to that used by Hamer et al[2] and Richards et al,[3] the prevalence of ventricular electrical instability, defined as the induction of 10 or more intraventricular reentrant beats, was 46% (higher than previously reported).

Green et al[1] found that 79% of patients with ventricular electrical instability had symptomatic VT or sudden death, or both, compared with 14% of these who did not have repetitive ventricular responses ($p < 0.001$). Hamer et al[2] found that patients with ventricular electrical instability had a significantly higher incidence of sudden death compared with patients without ventricular electrical instability ($p < 0.05$). Richards et al[3] found that ventricular electrical instability assessed by programmed ventricular stimulation was predictive of the development of spontaneous VT or sudden death during a mean follow-up of 8 months ($p < 0.001$). In a subsequent report, Holley et al,[7] from the same laboratory, showed that induction of VF in these patients was not associated with sudden death during follow-up. Marchlinski et al[5] and Borggrefe et al[6] failed to observe any correlation between ventricular electrical instability and sudden death, although in the study of Borggrefe, ventricular electrical instability was associated with subsequent development of sustained VT.

Although we found a high prevalence of ventricular electrical instability, no sudden death was observed during follow-up. The stable clinical condition (Killip class II or less) of our patients may account for the low mortality during follow-up. The absence of sudden death may be partially explained by aggressive treatment of 3 patients with spontaneous, symptomatic sustained VT: 1 had aneurysmectomy for intractable VT and 2 underwent serial electrophysiologic studies for selection of an antiarrhythmic drug regimen. Furthermore, 18% of our patients received antiarrhythmic drugs on an empiric basis. Although empiric antiarrhythmic therapy has not been demonstrated to reduce cardiac mortality after myocardial infarction, this possibility, using amiodarone, can not be completely ruled out in our study.

We conclude that in patients who are hemodynamically stable after acute myocardial infarction, (1) programmed ventricular stimulation can be safely performed; (2) there is a high prevalence of inducible sustained and nonsustained VT, which does not correlate with the clinical or angiographic data; (3) after discharge, those with ventricular electrical instability show a higher incidence of nonsustained VT during Holter monitoring than those without ventricular electrical instability; and (4) the predictive value of programmed ventricular stimulation in sudden death can not be addressed by our study because of low incidence of fatal events and high prevalence of therapy.

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Bretylium: Relations Between Plasma Concentrations and Pharmacologic Actions in High-Frequency Ventricular Arrhythmias

HENRY J. DUFF, MD, DAN M. RODEN, MD, AVRAHAM YACOBI, PhD, DAVID ROBERTSON, MD, THEODORE WANG, MD, REBECCA J. MAFFUCCI, RN, JOHN A. OATES, MD, and RAYMOND L. WOOSLEY, MD, PhD

Although it is widely assumed that the early arrhythmogenic and pressor responses to bretylium are caused by catecholamine release from the adrenergic neuron, this assumption has not been systematically studied in humans. Pharmacologic responses to a placebo infusion and 3 separate bretylium infusions (2.5, 5.0, 10 mg/kg over 60 minutes) were assessed in 6 patients with recurrent, nonsustained ventricular tachycardia. Plasma bretylium concentration, blood pressure (BP), plasma norepinephrine (NE) concentration, arrhythmia frequency and adrenergic neuronal blockade (assessed by the presence or absence of reflex venoconstriction) were measured. Adrenergic blockade was seen with every bretylium infusion and at a time when relatively small amounts of bretylium had been administered (range 160 to 750 mg, median 252). Temporal relations ($p < 0.03$) were noted among the time of onset of adrenergic neuronal blockade, onset of the pressor response, increase in NE plasma concentration and increase in ventricular arrhythmia frequency. BP responses during the infusions were linearly related to change in plasma NE at the time of development of adrenergic neuronal blockade. Bretylium plasma concentrations higher than 3 μg/ml were frequently associated with a short-lived pressor response. There was a significant relation ($p < 0.06$) between the increase in plasma NE during the infusion and an increase in ventricular arrhythmia frequency. Reduction in arrhythmia frequency was seen in only 1 patient, beginning 6 hours after the development of adrenergic neuronal blockade. In conclusion, soon after bretylium administration to patients with ventricular arrhythmias, a dose-related increase in BP and arrhythmia frequency occurred that were temporally related to catecholamine release and adrenergic neuronal blockade. Lack of antiarrhythmic response in this highly selected population does not detract from the proved efficacy of bretylium in patients with recurrent sustained ventricular tachycardia and fibrillation.

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From the Division of Clinical Pharmacology, Departments of Pharmacology and Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee. This study was supported by Grant 5M01-RR-95 from the General Clinical Research Center, Program of the Division of Research Resources, National Institutes of Health, Bethesda, Maryland; Grants GM15439 and GM07569 from the U.S. Public Health Service, Washington, D.C.; the Canadian Heart Foundation, Ottawa, Canada, and American Critical Care, New York, New York. Manuscript received January 27, 1984; revised manuscript received October 19, 1984, accepted October 23, 1984.

Address for reprints: Raymond L. Woosley, MD, PhD, Vanderbilt University Medical Center, Department of Pharmacology, Nashville, Tennessee 37232.

Bretylium, a quarternary ammonium compound, is effective in the treatment of life-threatening ventricular arrhythmias in humans.[1–5] Its widespread use has been limited by complex pharmacodynamic features,[6–11] including a short-lived initial "sympathomimetic" phase (associated with sinus tachycardia, positive inotropic effects[8,11] and local release of norepinephrine (NE) from adrenergic terminals in the heart[11] of dogs) followed by prolonged orthostatic hypotension due to adrenergic neuronal blockade.[8] Case reports indicate that the initial sympathomimetic phase is, at times, associated with

increase in ventricular arrhythmia frequency.[12,13] Although the early arrhythmogenic and pressor effects of bretylium are believed to be caused by catecholamine release, this had not been systematically evaluated in man. In this study 6 patients with high-frequency ventricular arrhythmias received 4 separate infusions in a randomized sequence; placebo and bretylium infusions of 2.5, 5 and 10 mg/kg. The relations among changes in ventricular arrhythmia frequency, plasma bretylium and NE concentrations, blood pressure (BP), electrocardiographic intervals and the presence or absence of adrenergic neuronal blockade were assessed.

Methods

Study design: Patients whose high-frequency ventricular arrhythmias were stable during prolonged recumbency and with no known reversible causes were candidates for this study. Patients with angina, congestive heart failure (New York Heart Association class III or IV), aortic stenosis, abnormal renal disease (creatinine clearance less than 60 ml/min), abnormal liver function or unstable concurrent illnesses were excluded. This study was approved by the Committee for the Protection of Human Subjects of Vanderbilt University and all patients gave informed consent. At least 4 half-lives after withdrawal of all medications, the frequency of ventricular premature complexes (VPCs) was determined during 3 hours of supine rest. If the supine arrhythmia frequency was greater than 120 VPCs/hour throughout this period, the patient was admitted to the study. All patients were maintained on a 2-g-sodium, caffeine-free diet.

Each patient received 4 separate infusions of placebo and bretylium (2.5, 5 and 10 mg/kg, supplied by American Critical Care) in a randomized sequence. The infusions were separated from each other by at least 48 hours and subsequent infusions were only given if both BP (standing and supine) and arrhythmia frequency had returned to baseline levels. To minimize the chance of a carryover effect, the randomization sequence did not permit the 10-mg/kg infusion to precede a 2.5-mg/kg or placebo infusion. Individual studies consisted of a 30-minute control period followed by a 30-minute placebo infusion (5% dextrose), followed by the 1-hour treatment infusion (placebo or bretylium). The infusions were administered with a Harvard model 600 pump. Clinical observations were made every 15 minutes during the control and dextrose infusion periods and every 5 to 15 minutes during treatments. These measurements included BP and pulse (both supine and 35° tilt), ventricular arrhythmia frequency, electrocardiographic intervals, plasma bretylium concentration, plasma NE concentration and the presence or absence of reflex venoconstriction (venous reflex response), described later. The PR, QRS, QT and RR intervals were measured after at least 5 consecutive sinus beats; rate corrected QT (QTc) was calculated from the formula $QTc = QT/\sqrt{RR}$. After the treatment periods, electrocardiographic data were continuously recorded for 48 hours.

Arrhythmia frequency: Electrocardiograms were recorded from a telemetry signal on a Honeywell model 96, FM, 8-channel recorder. The taped data were then analyzed by a computer operator, who was blinded to the treatment being given, using a PDP 11/60 minicomputer and a previously described and verified template-matching program.[14] This system quantifies the number of VPCs, ventricular couplets and runs of ventricular tachycardia (VT) (more than 3 consecutive VPCs at a cycle length shorter than 600 ms).

The change in arrhythmia frequency during bretylium infusions was established by a comparison to the arrhythmia frequency seen during the 1-hour placebo infusion. Late antiarrhythmic and electrocardiographic changes were sought by comparing electrocardiographic data during the first 6 and second 6 hours after the bretylium infusions to the corresponding hours after placebo infusion.

Pharmacokinetic assessment: Plasma samples for analysis of bretylium concentration and vital signs (BP and pulse, supine and sitting) were obtained at 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36 and 48 hours after beginning the bretylium infusions. The plasma concentrations were fitted to a 2-compartment open model incorporating a 1-hour infusion period, using the program NONLIN. The negative slope (elimination constant, Kel) was calculated from the best fit for the terminal portion of the time-log concentration plot. The area under the curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity. Systemic clearance was calculated using the formula: clearance = dose/AUC. A gas-liquid chromatographic system was used to quantify bretylium concentrations in plasma.[15] Plasma NE concentrations in plasma were quantified using a radioenzymatic assay.[16]

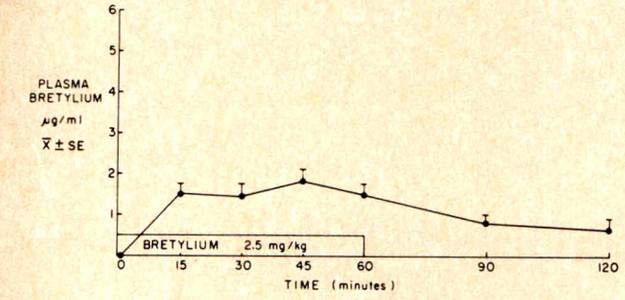
Venous reflex response: A 19-gauge intravenous cannula was introduced into a superficial vein on the dorsum of the hand and connected to a calibrated pressure transducer. A pediatric BP cuff was placed at the wrist and inflated to 300 mg Hg. This effectively isolates the hand from the circulation, yet leaves the vein capable of responding to neural stimuli.[17,18] The stimulus used to elicit reflex venoconstriction in this study was a deep breath.[19] Loss of the venous reflex response has been documented with the use of adrenergic blocking drugs such as guanethidine. The presence or absence of reflex venoconstriction was assessed at least once during the control period, once during the dextrose infusion and every 5 to 15 minutes during treatment.

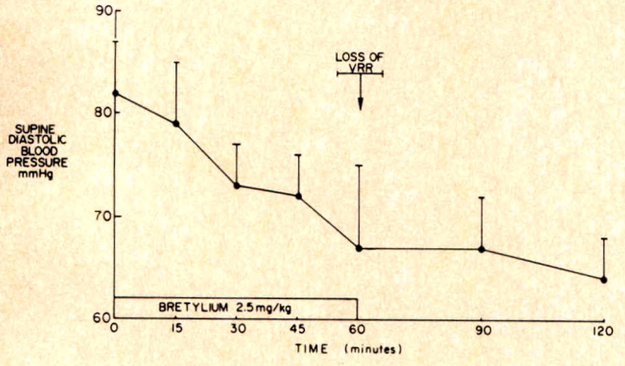
Results

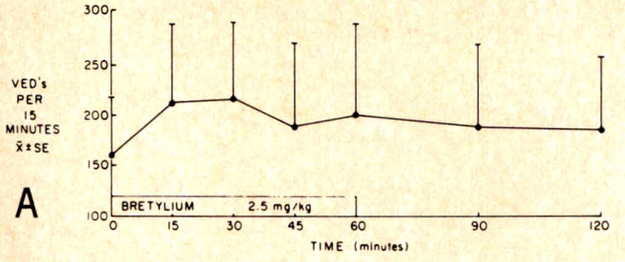
Six men, aged 42 to 64 years (mean 54), participated in this study: 2 with hypertensive heart disease, 2 with ischemic heart disease and the 2 with no known structural heart disease. Twenty-two other patients were considered but were excluded because of marked time-dependent decrease in ventricular arrhythmia frequency during recumbency. None of the 6 selected patients received medications other than bretylium or placebo during this study. All patients had short bursts of self-limited VT during ambulatory monitoring that were resistant to conventional antiarrhythmic agents. Group mean arrhythmia frequency during the control dextrose infusion was 558 ± 223 VPCs/hour (± standard deviation), with 37 ± 29 couplets and 0.4 ± 0.3 episodes of VT per hour. A similar arrhythmia frequency was seen during the subsequent 1-hour placebo infusion (339 ± 145 VPCs with 27 ± 22 couplets and 0.4 ± 0.3 episodes of VT), indicating the relative stability of arrhythmia frequency during this time.

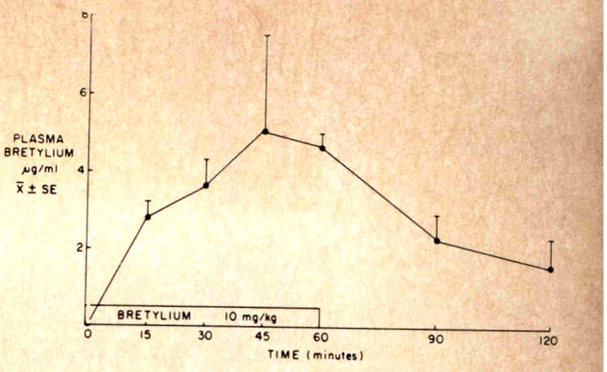
Adrenergic neuronal blockade: The overall pharmacodynamic features are presented in Figure 1. Adrenergic neuronal blockade developed in all patients during bretylium infusions, but at 62 ± 12 minutes with the 2.5-mg/kg dose; 33 ± 4 minutes with the 5.0-mg/kg dose; and 35 ± 15 minutes with 10/mg/kg infusion. Figure 2 shows the cumulative proportion of subjects who lost the venous reflex response (development of adrenergic neuronal blockade) in relation to the dosage of bretylium administered at that time.

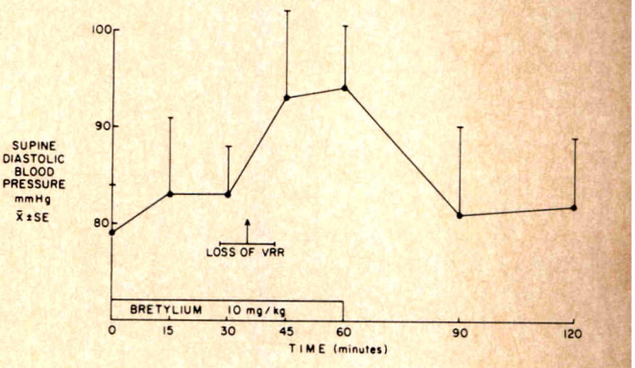
Pressor response: Figure 1 illustrates plasma concentrations of bretylium relative to changes occurring in BP. There was a nonsignificant decrease in BP with the 2.5-mg/kg infusion. In contrast, the 10-mg/kg infusion of bretylium resulted in higher concentrations of bretylium and a significant pressor response ($p < 0.05$). Low-dose bretylium infusion was associated with a reduction in plasma NE, while high-dose infusion resulted in increase in plasma NE and an associated pressor response. Figure 3 illustrates the strong temporal relation among the onset of the pressor response, NE release and adrenergic neuronal blockade. A linear relation was also noted between bretylium concentration at time of loss of the venous reflex response and the extent of subsequent change in BP ($r = 0.65$, $p < 0.01$). Subjects with plasma bretylium concentrations greater than 3 μg/ml at the time of loss of venous reflex response generally had a pressor response. A relation was also noted between maximal change in BP during the

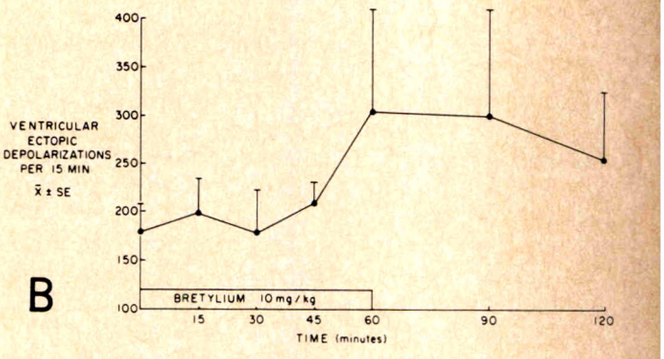


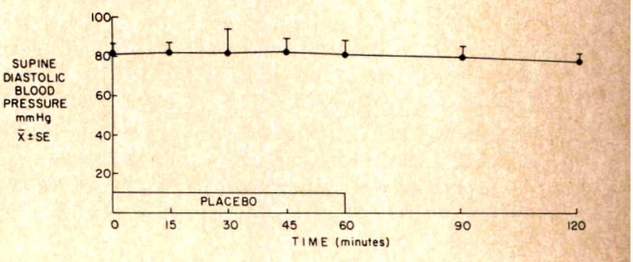












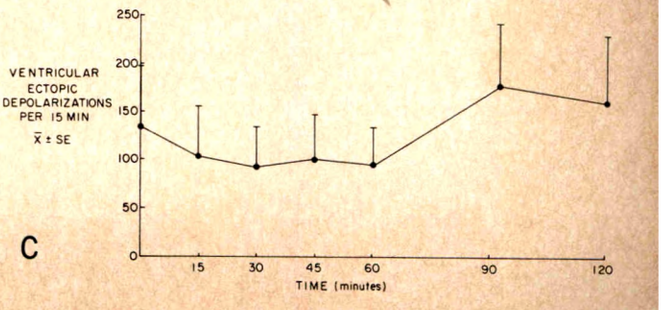


FIGURE 1. Plasma concentrations of bretylium, changes in blood pressure, ventricular arrhythmias and the time of loss of the venous reflex (VRR) during infusion of 2.5 mg/kg (**A**) and 10 mg/kg (**B**) of bretylium and (**C**) placebo. SE = standard error; VED = ventricular ectopic depolarization.

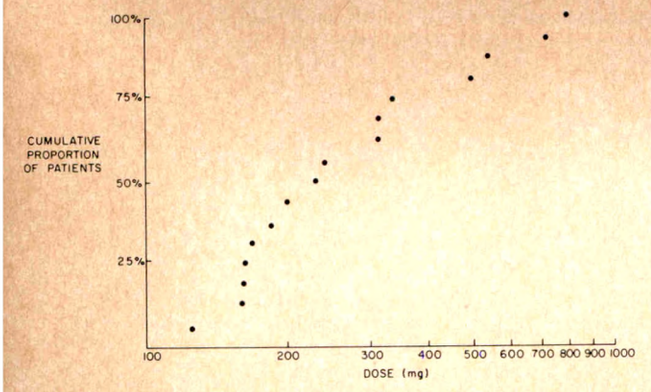


FIGURE 2. The cumulative proportion of patients who had lost the venous reflex response in relation to the dosage of bretylium given by that time.

bretylium infusion and maximal change in NE concentration occurring over the same period (Fig. 4) ($r = 0.82$, $p < 0.01$)].

Arrhythmia frequency: The 2.5-mg/kg bretylium infusion was not associated with a change in arrhythmia frequency, while the 10 mg/kg infusion resulted in a short-lived significant increase in frequency of PVCs, ventricular couplets and VT. Table I illustrates the significant relation ($p < 0.06$) between presence or absence of increase in plasma NE (>50 pg/ml above the control) during the infusion to presence or absence of worsening of ventricular arrhythmias (defined as a 100% or greater increase in VPC frequency relative to control, paralleled by an increase in ventricular couplets or by the onset of episodes of VT not seen during control observations). Although there is an association between these variables, several subjects had discordant results; worsening of ventricular arrhythmias did occur in the absence of measurable increases in plasma NE in 4 of 17 infusions.

The only patient who had frequent episodes of VT was also the only patient who had an antiarrhythmic response to bretylium, beginning 6 hours after the bretylium infusion was stopped. This delayed antiarrhythmic effect coincided temporally with development of electrocardiographic interval changes.

Electrocardiographic interval changes: No changes were seen in QRS duration and QTc during or after bretylium infusions in any of the patients. However, during the early sympathomimetic period (10-mg/kg infusions), shortening of the sinus cycle length (i.e., increased heart rate) was associated with shortening of the coupling interval of the predominant ventricular premature template (Fig. 5A). Also, beginning 6 hours after stopping the bretylium infusion, prolongation of the coupling interval of the predominant ventricular premature template was seen (Fig. 5B).

Pharmacokinetic parameters: A nonlinear relationship was noted between administered dose and resultant area under the plasma concentration curve, and clearance appears to increase with dose (Table II). No significant dose-dependent changes in Kel were noted. Peak plasma concentrations during the 2.5, 5.0 and 10 mg/kg infusions were 1.8 ± 4.5, 3.2 ± 0.8 and 5.0

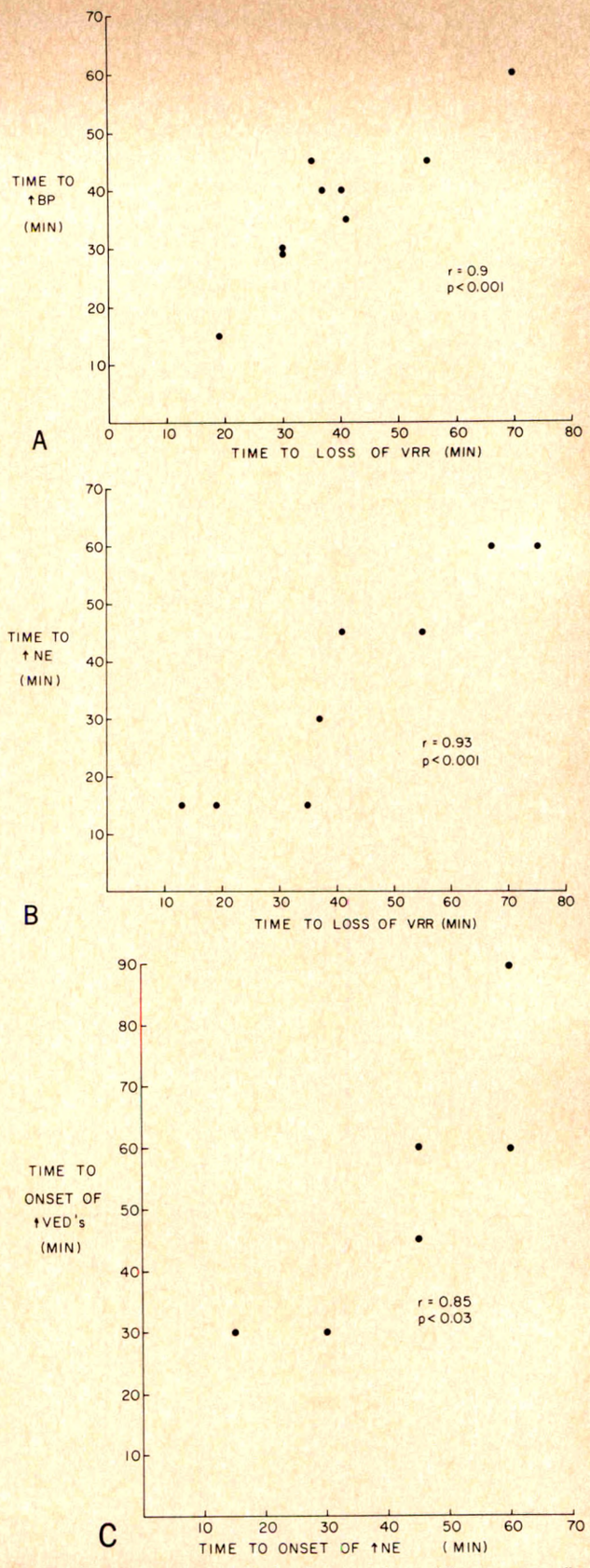


FIGURE 3. The temporal relation between loss of the venous reflex response (VRR) and (**A**) the onset of a pressor response, (**B**) onset of norepinephrine (NE) release, and (**C**) temporal relation between onset of arrhythmia worsening and onset of norepinephrine release. BP = blood pressure; VED = ventricular ectopic depolarization.

± 3.6 μg/ml (mean ± standard deviation), respectively.

Side effects: Nausea occurred in 3 patients, all during the 10 mg/kg infusion and at a mean plasma concentration of 5.3 ± 0.9 μg/ml. All patients had orthostatic hypotension after the bretylium infusions.

Discussion

Data from animal models suggest that bretylium is taken up by the amine pump in the adrenergic neuron and blocks subsequent release of catecholamines mediated by neuronal discharge.[8,20] In this study in man, adrenergic neuronal blockade occurred after relatively small dosages of bretylium—doses less than those generally required to suppress ventricular arrhythmias under clinical conditions. These findings are in agreement with other experimental and clinical data, suggesting that the antiarrhythmic actions of bretylium are independent of neuronal blockade.[1,21–23] Evidence for direct antiarrhythmic effects include the absence of antifibrillatory effects seen with sympatholytic interventions such as catecholamine depletion with reserpine or adrenergic blockade with quanethidine; continued clinical antiarrhythmic effects of bretylium when adrenergic neuronal blockade is reversed by the addition of a tricyclic antidepressant[24]; and the delayed onset of antiarrhythmic effect[4] well after the development of adrenergic neuronal blockade. In keeping with this concept, the only subject in this study who had an antiarrhythmic response had it 6 hours after the development of adrenergic neuronal blockade. The delayed onset of this antiarrhythmic effect may parallel a delayed myocardial accumulation of bretylium, which has been reported to peak 3 to 12 hours after acute administration.[25] We also noted a similar delayed electrocardiographic effect, consisting of an increase in the coupling interval of the predominant ectopic focus, which may be a marker of bretylium's direct myocardial effect.

Animal studies indicate that bretylium initially causes a displacement of catecholamines from the terminal storage vesicles of the adrenergic neuron[8–11] and that the extent of release appears to be dose-dependent.[26] This study supports the concept that this same construct also applies in man. Pressor effects often occurred when plasma bretylium concentrations were greater than 3 μg/ml and the extent of change in BP was linearly related to change in plasma NE. The strong temporal relations among onset of the pressor response, NE release and adrenergic neuronal blockade also supports the concept of catecholamine displacement.

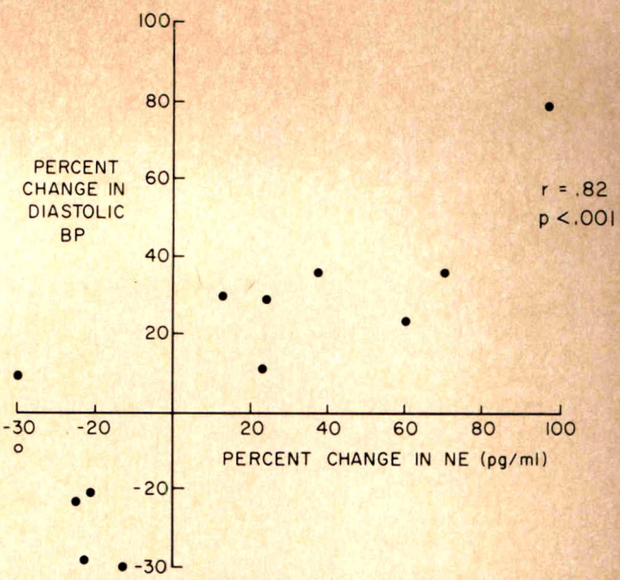


FIGURE 4. Linear relation between maximal changes in blood pressure (BP) and norepinephrine (NE) concentration during bretylium infusion.

Because of the sporadic nature of ventricular arrhythmias, the initial worsening of arrhythmia frequency was established by several criteria. First, a dose-response relation was seen during the administration of increasing dosages. Second, the increase in ventricular ectopic depolarizations was generally paralleled by an increase in frequency of ventricular couplets and episodes of nonsustained VT. Third, during placebo infusions (over the same time period), worsening of ventricular arrhythmias were not observed. Although isolated case reports have suggested that bretylium could precipitate the development of sustained VT during its early sympathomimetic phase,[13]

TABLE I Relation Between Norepinephrine Release and Arrythmia Frequency

	NE Increased	NE Unchanged	
Arrhythmias increased	7	2	
Arrhythmias unchanged	1	3	
	8	5	13

$p < 0.06$, χ^2.
NE = norepinephrine.

TABLE II Pharmacokinetics

	Dosage (mg/kg)		
	2.5	5.0	10
βKel (hr^{-1})	0.04 ± 0.02	0.03 ± 0.01	0.04 ± 0.01
Half-life (hr)	21 ± 9	23 ± 9	19 ± 7
AUC (mg·hr/liter)	15 ± 11	25 ± 20	30 ± 15
Total systemic clearance (CL) (liters/hr)	20 ± 9	24 ± 13	32 ± 10
CL/kg (liters/kg·hr)	0.25 ± 0.15	0.29 ± 0.16	0.4 ± 0.16

AUC = area under the curve; βKel = elimination constant.

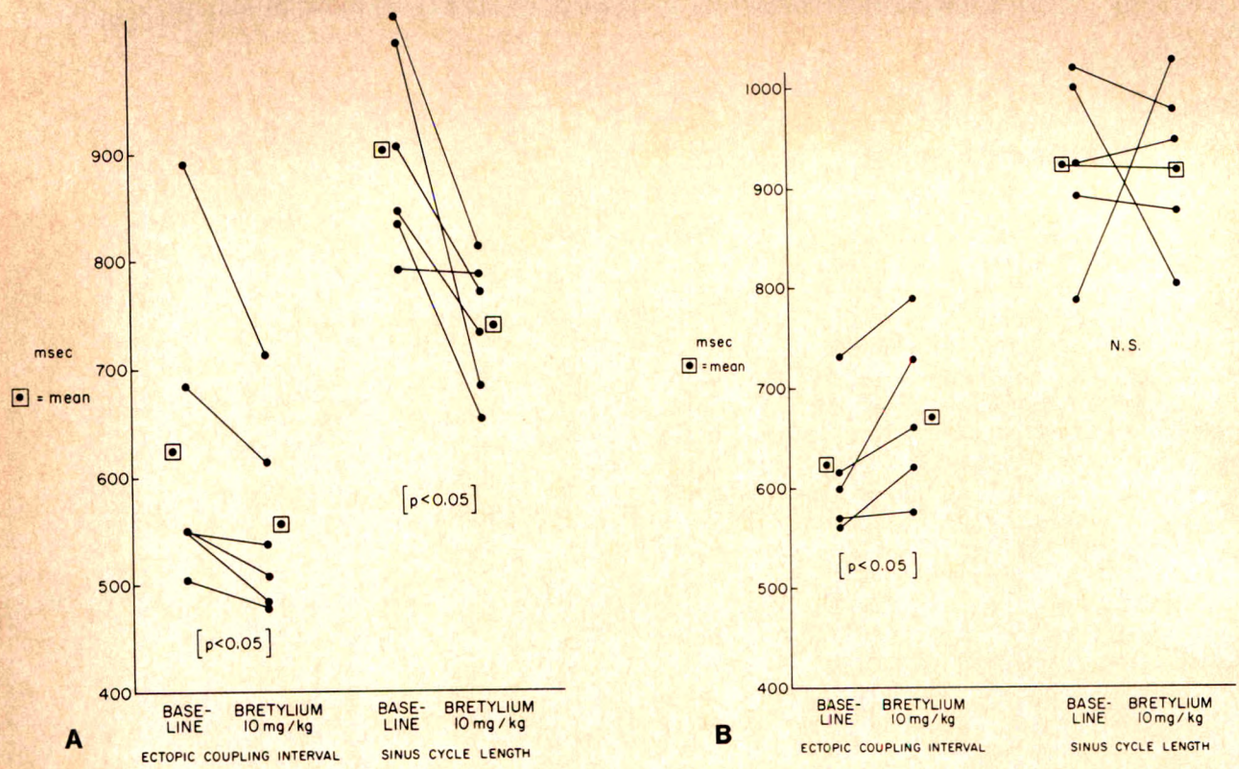


FIGURE 5. The change in coupling interval of the predominant ectopic focus (**A**) during the early sympathomimetic period and (**B**) 6 to 12 hours after the infusion. N.S. = not significant.

in this study episodes of VT were limited to 5-beat salvos in 1 patient and only triplets occurred in the other patients.

While substantial evidence exists for the efficacy of bretylium in the treatment of resistant VT or ventricular fibrillation, bretylium has not been convincingly effective in the treatment of high-frequency chronic ventricular arrhythmias. In the study by Romhilt et al,[27] 5 of 8 patients had a 50% or greater suppression of ventricular ectopic beats over placebo on 24-hour recordings. However, an 83% reduction in VPCs is required to distinguish a true antiarrhythmic response from spontaneous variability.[28] In the present study, no antiarrhythmic response was seen either early or late in 5 of the 6 patients. Bretylium's lack of ability to suppress VPCs may relate to its electrophysiologic actions. Unlike many other antiarrhythmic agents, bretylium does not affect conduction velocity, increase the ratio of ventricular effective refractory period to action potential duration or depress automaticity.[29,30] Bretylium's antiarrhythmic and antifibrillatory effects may relate to its ability to reverse maintenance factors that allow arrhythmias to become sustained (dispersion of repolarization between ischemic and normal ventricular tissue[30]). While this pharmacologic effect may suppress VT and ventricular fibrillation, it may not suppress simple VPCs.

In conclusion, bretylium produces a dose-related increase in BP and arrhythmia frequency that is short-lived and is temporally related to cathecholamine release and adrenergic neuronal blockade.

Acknowledgment: We are indebted to Brenda Mullinger, Gregory Douglas and Judith Osman for assistance in the preparation of this manuscript.

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Continuous Electrical Activity During Sustained Monomorphic Ventricular Tachycardia

Observations on Its Dynamic Behavior During the Arrhythmia

PEDRO BRUGADA, MD, HOSHIAR ABDOLLAH, MD, and HEIN J. J. WELLENS, MD

Catheter mapping was performed during sinus rhythm and monomorphic ventricular tachycardia (VT) in 56 consecutive patients with sustained, monomorphic VT. Forty-two patients had an old myocardial infarction (VT-old MI group), 6 patients had right ventricular dysplasia (VT-RV dysplasia group), and 8 patients had idiopathic VT (idiopathic-VT group). Continuous electrical activity was recorded in 15 of 42 patients of the VT-old MI group (36%), 5 of 6 of the VT-RV dysplasia group (83%), and in 0 of 8 patients in the idiopathic VT group (0%). In 17 of 20 patients with continuous electrical activity during VT, observations on the dynamic behavior of continuous electrical activity during VT revealed at least 1 of the following characteristics: (1) spontaneous disappearance and reappearance of continuous electrical activity without changes in rate, morphologic pattern or axis of VT; (2) pacing-induced transient termination of continuous electrical activity without termination of VT; (3) spontaneous disappearance of continuous electrical activity during VT as a rate-dependent phenomenon; (4) Wenckebach-like conduction to other areas resulting in transient and periodic continuous electrical activity; (5) dependence of continuous electrical activity on ventricular activation pattern during VT; (6) pacing-induced change from a noncontinuous electrogram into continuous electrical activity without prevention of termination of VT; and (7) termination of continuous electrical activity after antiarrhythmic drugs without termination of VT. Continuous electrical activity was always recorded in the aneurysm and never over normal heart areas. At the sites where continuous electrical activity was recorded during VT, potentials recorded during sinus rhythm were abnormal. Our observations suggest that several electrophysiologic phenomena can simulate continuous electrical activity during monomorphic VT. Transient, continuous electrical activity is a frequent phenomenon that represents electrical activity from abnormal areas not necessarily required to perpetuate VT.

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Since the early studies on experimental atrial flutter by Sir Thomas Lewis,[1] mapping of electrical activity of the heart has been extensively used in the experimental and clinical laboratory. Several investigators, using mapping techniques, have demonstrated the reentrant nature of a variety of arrhythmias.[2–7] Application of the information from experimental studies to the clinical situation has resulted in the development of new surgical techniques for treatment of patients with arrhythmias.[8–13] However, the interpretation of the results of clinical mapping still remains difficult. Long-lasting electrical activity is expected to be registered when recording is done directly from a reentrant circuit. It has been questioned, however, that the recording of electrical activity spanning the cardiac cycle (continuous electrical activity) always proves that the catheter is located at the site of the reentry circuit.[7,14,15] Continuous electrical activity has not been clearly defined qualitatively or quantitatively. To investigate the incidence and significance of electrical activity spanning the cardiac cycle during catheter mapping of monomorphic ventricular tachycardia (VT), a prospective study was undertaken in 56 patients. In these patients the dynamic behavior of endocardial electrical activity during VT was studied.

From the Department of Cardiology, University of Limburg, Annadal Hospital, Maastricht, The Netherlands. Manuscript received August 3, 1984; revised manuscript received October 24, 1984, accepted October 25, 1984.

Address for reprints: Pedro Brugada, MD, Clinical Electrophysiology Laboratory, Department of Cardiology, University of Limburg, Annadal Hospital, Maastricht, The Netherlands.

Methods

Fifty-six consecutive patients with clinically documented, sustained, monomorphic VT were studied. Their clinical data are given in Table I. Forty-two patients had an acute myocardial infarction (MI) 3 weeks to 13 years before study (VT-old MI group). Their first episode of VT developed 6 days to 6 years after MI. Six patients had the syndrome of right ventricular (RV) dysplasia (VT-RV dysplasia group). In 8 patients no abnormalities were found to explain the cause of their VT (idiopathic-VT group). No patient with ventricular fibrillation or polymorphic VT, was included in the study.

Each patient gave informed consent. The 56 patients then underwent an electrophysiologic investigation using previously described methods of stimulation, recording and analysis of tracings.[16] All antiarrhythmic drugs were stopped at least 72 hours before study. After the mode of initiation and termination of VT was assessed, mapping of right and left ventricular endocardial activation was performed during sinus rhythm. Eight to 20 right and left ventricular sites were mapped. The catheter used was a quadripolar electrode (Josephson catheter, USCI) with an interelectrode distance of 0.5 cm. Recordings were made from electrodes 1 to 3 and

TABLE I Clinical Data on 56 Patients

	n	Age (yr)	Sex (M/F)
Old MI*	42	37–73	39/3
RV dysplasia	6	27–40	6/0
Idiopathic VT	8	18–54	5/3

* Anterior in 28, inferoposterior in 14.
MI = myocardial infarction; RV = right ventricular; VT = ventricular tachycardia.

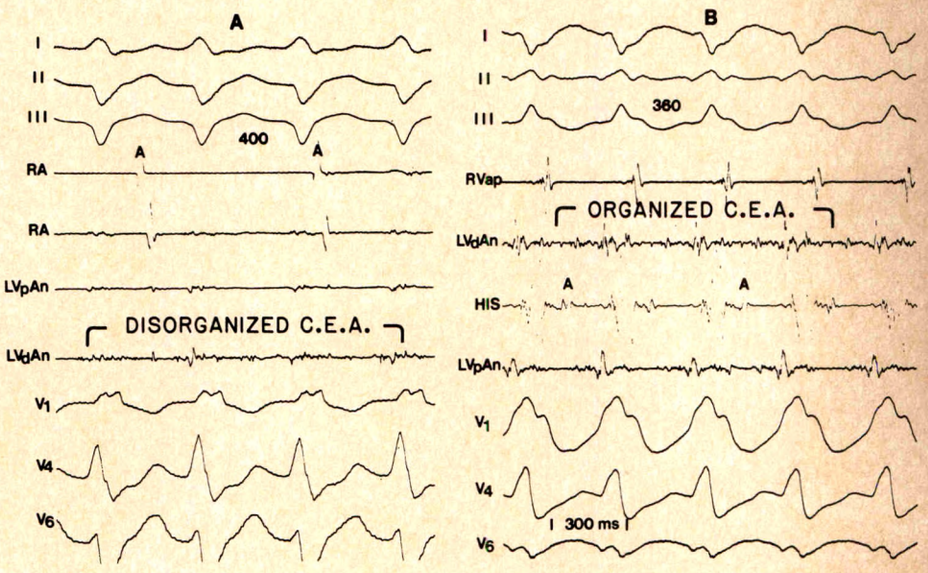

FIGURE 1. The 2 types of continuous electrical activity (C.E.A.) observed during ventricular tachycardia. **A,** disorganized continuous electrical activity in the distal left ventricular recording from the aneurysm (LV_dAn). **B,** regular repetitive pattern of continuous electrical activity (organized continuous electrical activity) in the LV_dAn. Six surface leads are simultaneously shown, with bipolar electrograms from the right atrium (RA), right ventricular apex (RVap), His bundle and proximal (p) and distal (d) LVAn.

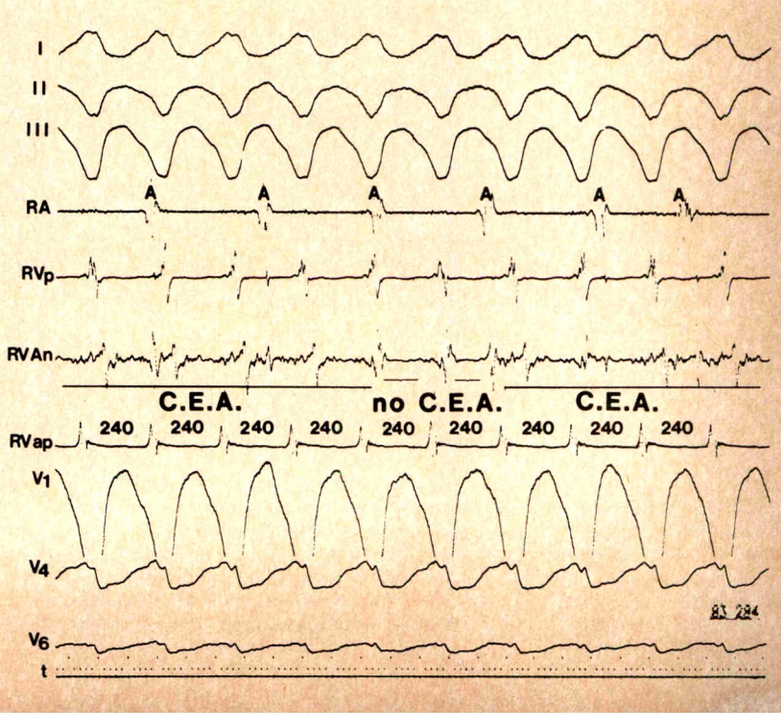

FIGURE 2. Spontaneous disappearance and reappearance of continuous electrical activity (C.E.A.) during ventricular tachycardia (VT) without changes in rate or morphologic pattern of VT in a patient with right ventricular (RV) dysplasia. In the **left** and **right** part of the figure, continuous electrical activity is recorded in the bipolar recording from an RV aneurysm (RVAn). In the **middle** part of this tracing, continuous electrical activity disappears, without changes in VT. Six surface leads are shown simultaneously recorded with bipolar electrograms from the right atrium (RA), proximal right ventricle (RVp), RV aneurysm (RV An) and RV apex (RVap).

2 to 4 in order to obtain 2 bipolar electrograms (1-cm interelectrode distance) which were separated 0.5 cm from each other. In patients with localized wall motion abnormalities, mapping was always started over the normal heart areas. Thereafter, mapping was performed inside the aneurysm. When abnormal potentials (<1 mV, duration >50 ms, or occurring after the end of the QRS complex in the surface leads) were present during sinus rhythm the catheter, was positioned at this site and in this position VT initiated. The effect of timed ventricular premature beats and overdrive ventricular pacing on the abnormal potentials during VT was then studied. The same procedure was repeated at other ventricular sites. This was also done during intravenous administration of an antiarrhythmic agent, when possible. The catheter position and stability were frequently controlled by biplane fluoroscopy. All recorded electrograms were filtered between 40 and 500 Hz. The gain was adjusted as low as possible, with a maximum at 1 mV = 3 cm.

Continuous electrical activity was defined as the presence of electrical activity bridging 2 consecutive QRS complexes during VT. Double potentials during VT clearly separated by an isoelectric line were not considered to represent continuous electrical activity, but continuous electrical activity was diagnosed in 1 patient showing 3 potentials separated by an isoelectric line during 1 VT cycle.

Results

Incidence and types of continuous electrical activity: Diastolic activity after the QRS complex but not completely bridging the distance between 2 consecutive QRS complexes was observed during VT in all 42 patients in the VT-old MI group, all 6 patients in the VT-RV dysplasia group, and in none of the 8 patients of the idiopathic VT group. Continuous electrical activity during monomorphic VT was recorded in the left ventricle in 15 patients (36%) from the VT-old MI group, in 5 (83%) from the right ventricle in the RV

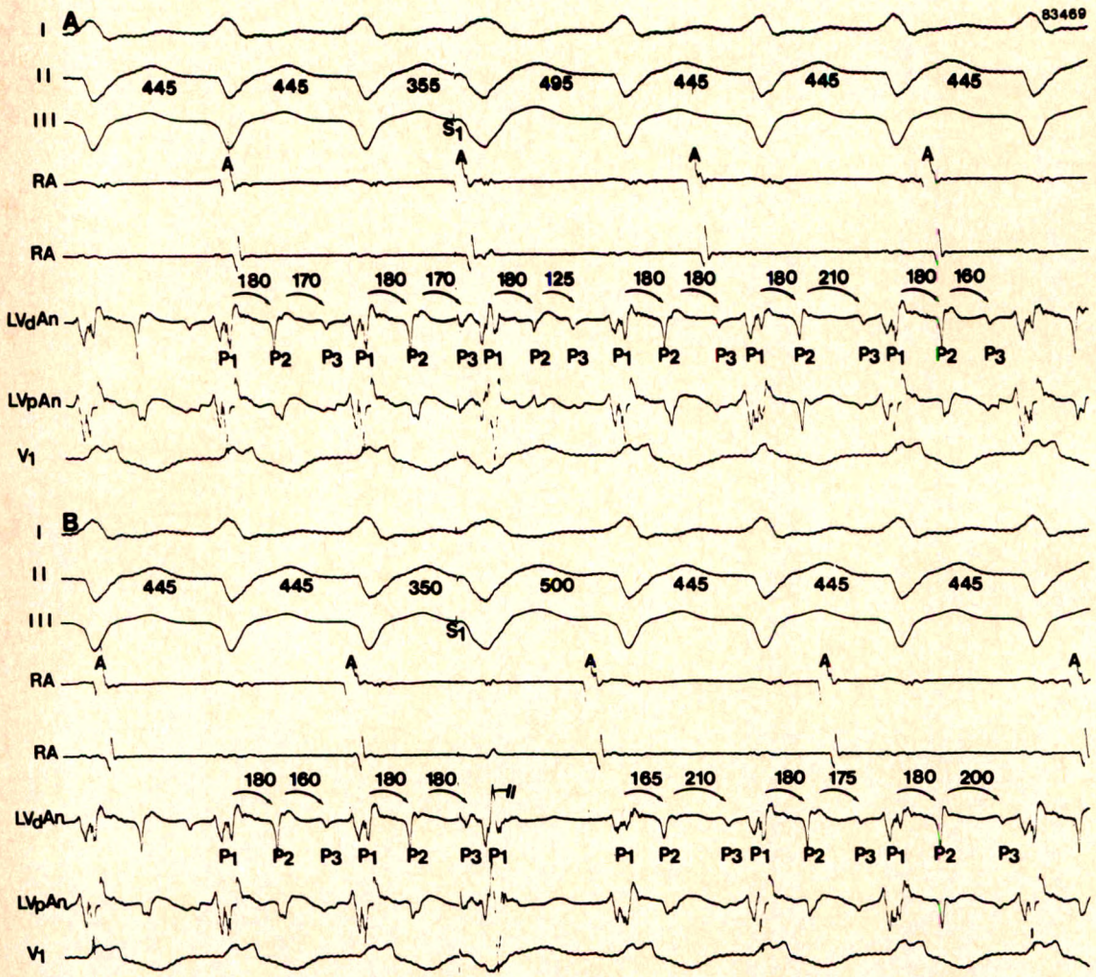

FIGURE 3. The effect of a single ventricular premature beat (S_1) on continuous electrical activity during ventricular tachycardia (VT). Three potentials (P_1, P_2 and P_3) are present on the distal left ventricular recording from the aneurysm (LV_dAn) during VT. **A,** an S_1 given after 355 ms does not terminate VT, but clearly changes the intervals between P_1, P_2 and P_3. Alternation in the P_2-P_3 interval from 160 to 210 ms is thereafter observed. This does not influence the cycle length or morphologic pattern of VT. **B,** an S_1 given 5 ms earlier than that in panel **A** (350 ms) does not terminate tachycardia, but P_1 is not followed by P_2 or P_3. These potentials reappear in the next VT cycles, again showing alternation in the P_2-P_3 interval. The P_1-P_2 interval is shorter after the pause produced by S_1. From these observations one may conclude that P_2 and P_3 are not an essential link in the VT circuit. Four surface leads are shown that were recorded simultaneously with 2 bipolar electrograms from the right atrium (RA) and the left ventricular aneurysm (LVAn). P = proximal.

dysplasia group and in no patient from the idiopathic-VT group.

Two types of continuous electrical activity were identified. Disorganized continuous electrical activity was characterized by a chaotic pattern of electrical activity throughout the cardiac cycle (Fig. 1A). Organized continuous electrical activity was characterized by a recognizable regular or repetitive pattern (Fig. 1B). Organized continuous electrical activity was more frequently recorded than disorganized continuous electrical activity. Seventeen out of the 20 patients who showed continuous electrical activity had an organized pattern and 6 of the 20 a disorganized pattern. Thus, 3 patients both an organized and disorganized pattern of continuous electrical activity was observed.

Observations on the dynamic behavior of continuous electrical activity: With the catheter positioned in a stable position against the ventricular wall, the dynamic behavior of continuous electrical activity was studied.

Spontaneous disappearance and reappearance of continuous electrical activity without changes in rate of VT, QRS complex morphology or axis: Before an antiarrhythmic drug was given, continuous electrical activity was observed to disappear and reappear spontaneously without change in rate, QRS morphologic pattern or axis of VT in 10 patients (Fig. 2). In 1 other patient, this phenomenon occurred after administration of intravenous procainamide. Spontaneous disappearance of continuous electrical activity occurred in 8 patients in the VT-old MI group and in 2 in the VT-RV dysplasia group.

Pacing-induced transient termination of continuous electrical activity during VT without termination of VT: In 5 patients (4 in the VT-old MI group and 1 patient in the VT-RV dysplasia group) ventricular stimulation during VT could transiently terminate continuous electrical activity (Fig. 3) without terminating VT. This was observed in 1 patient with triple potentials during VT in the aneurysm (Fig. 3), in 3 patients with organized continuous electrical activity (Fig. 4), and in 1 patient with disorganized continuous electrical activity. The phenomenon was induced by 1 to 3 ventricular premature beats in 3 patients, by overdrive ventricular pacing in 1 patient, and both by ventricular premature beats and overdrive pacing in 1 patient.

Continuous electrical activity as a rate-dependent phenomenon during spontaneous or pacing-induced changes in VT rate: In 7 patients (6 in the VT-old MI group and 1 in the VT-RV dysplasia group), continuous electrical activity appeared or disappeared as a rate-dependent phenomenon during spontaneous or pacing-induced changes in VT rate. In 2 patients this occurrred without changes in QRS configuration (Fig. 5).

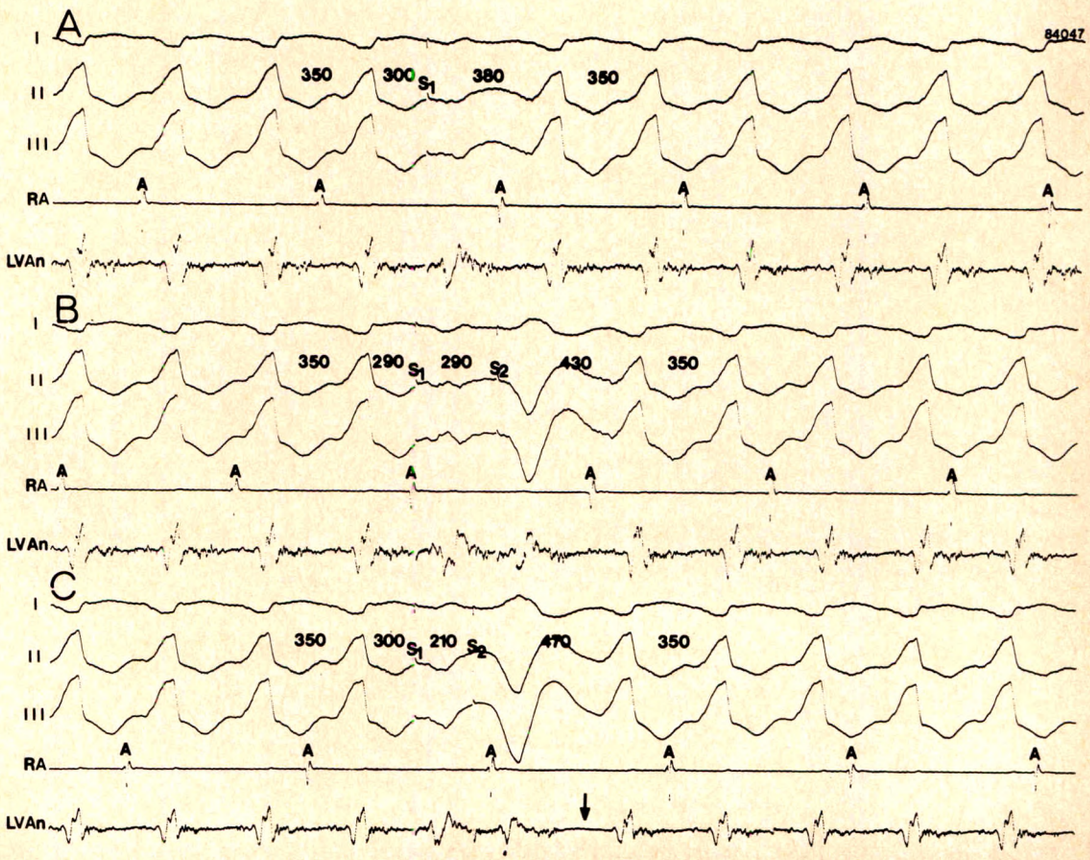

FIGURE 4. Termination of organized continuous electrical activity by premature beats given during ventricular tachycardia (VT). **A,** a ventricular premature beat (S_1) does not terminate continuous electrical activity and VT continues. **B,** 2 ventricular premature beats (S_1, S_2) also fail to terminate continuous electrical activity or VT. **C,** when the interval between S_1 and S_2 is shortened, continuous electrical activity is transiently terminated (**arrow**) without terminating VT.

In the other 5 patients this was observed during changes in VT rate and QRS configuration. Study of the duration of the electrograms during the slowest rate of VT suggested that continuous electrical activity during the fastest VT was probably the result of superposition of similar abnormal electrograms because of the increase in rate. In all 7 patients these observations were made during the organized type of continuous electrical activity.

Continuous electrical activity resulting from Wenckebach-like conduction: In 4 patients continuous electrical activity was simulated by a Wenckebach-like conduction pattern. This phenomenon resulted in an organized pattern of continuous electrical activity, which disappeared spontaneously for a few cycles, to return with regular periodicity (Fig. 6). The 2 closely located recording[s] allowed analysis of this phenomenon because more discrete signals were recorded from 1 pair at the same time that an organized pattern of continuous electrical activity was observed in the other pair of electrodes. In these 4 patients, changes in continuous electrical activity at 1 recording pair of electrodes closely paralleled changes in discrete potentials at the other pair. The fact that conduction block could occur to certain areas resulting in continuous electrical activity or multiple diastolic potentials without influencing the rate or morphologic pattern of VT demonstrates that conduction to these areas was not required to perpetuate VT.

Dependency of continuous electrical activity on the ventricular activation pattern during VT: Continuous electrical activity was not only a rate-dependent phenomenon, but was also critically dependent on the ventricular activation pattern during VT. Minimal changes in QRS morphologic pattern during VT resulted in initiation of the Wenckebach-like sequences

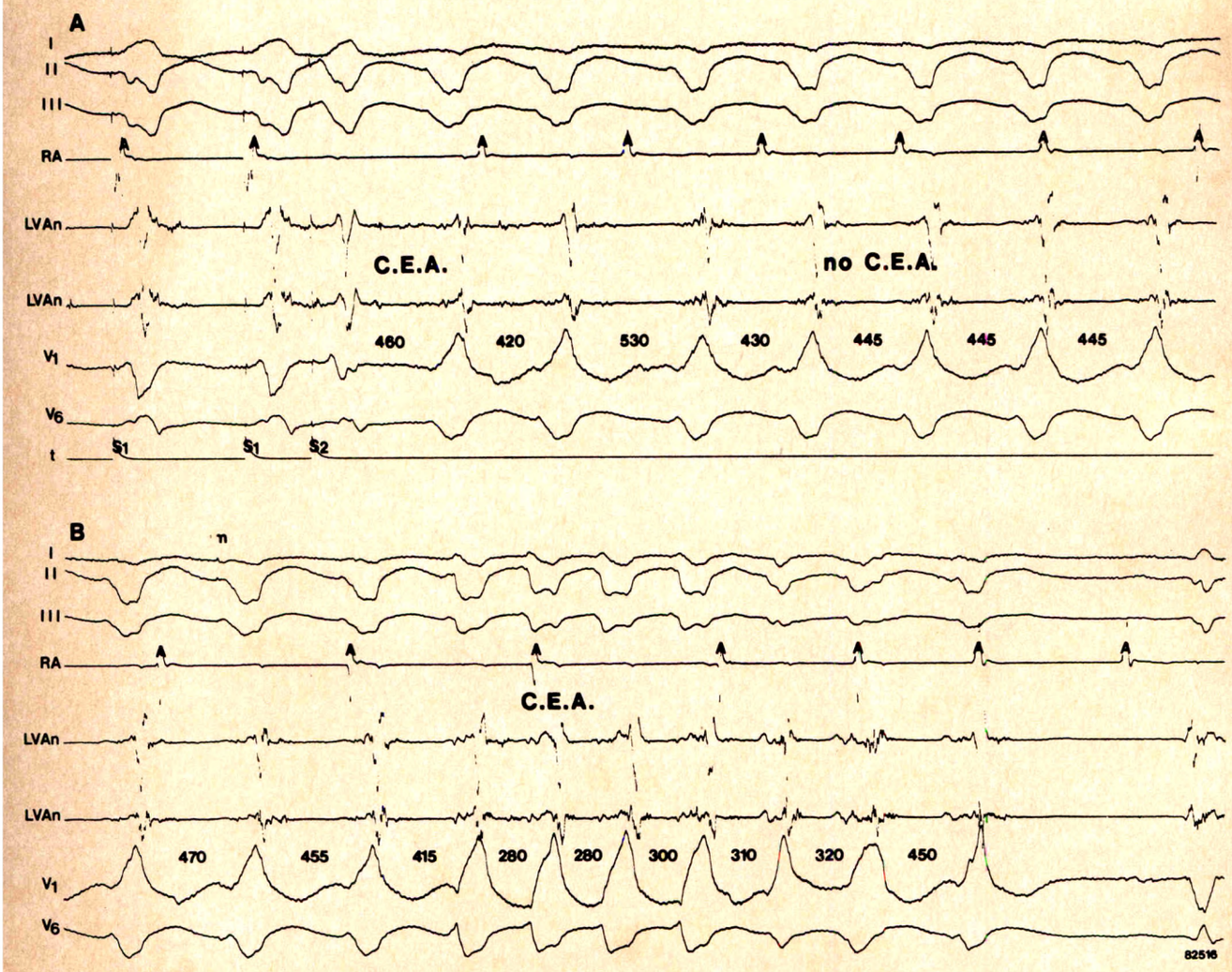

FIGURE 5. Continuous electrical activity (C.E.A.) during ventricular tachycardia (VT) as a rate-dependent phenomenon. **A,** a VT showing marked spontaneous changes in cycle length is initiated by 1 ventricular premature beat given during right ventricular pacing at 120 beats/min. Continuous electrical activity is observed at the onset of VT, but disappears spontaneously after the second VT cycle when the VT cycle length prolongs. **B,** spontaneous termination of the same episode of VT. VT suddenly accelerates before terminating. Continuous electrical activity is observed again when the VT cycle length reaches 280 ms. LVAn = left ventricular aneurysm; RA = right atrium.

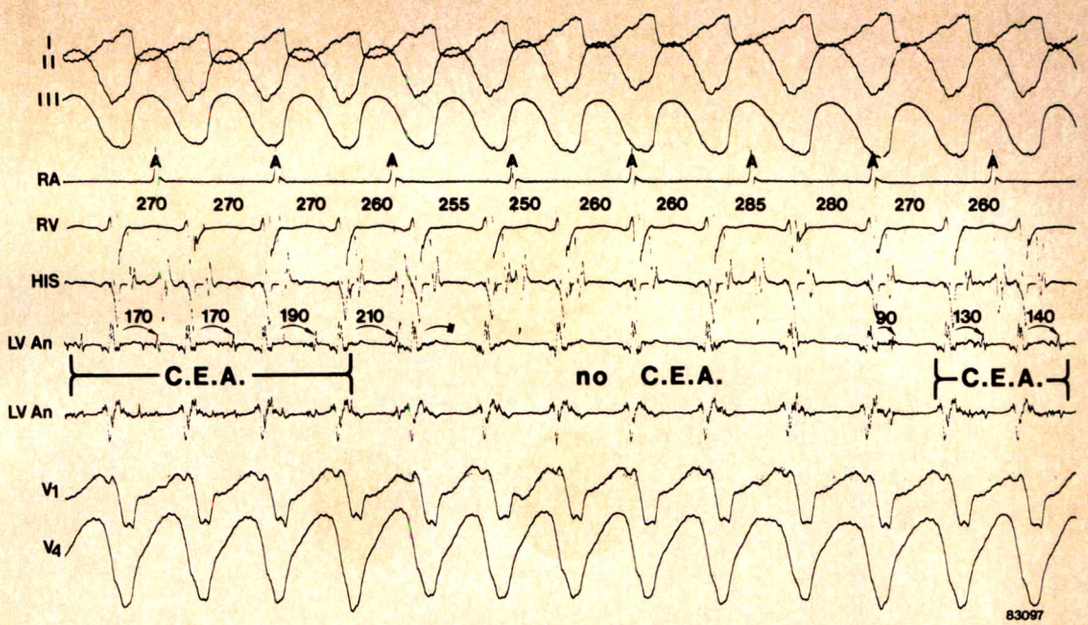

FIGURE 6. Spontaneous appearance and disappearance of continuous electrical activity (C.E.A.) resulting from Wenckebach-like conduction. During a ventricular tachycardia with minimal variations in cycle length (250 to 280 ms), continuous electrical activity is present at the left ventricular aneurysm (LVAn) in the **left** and **right** part of the figure, but absent in the **middle.** Analysis of the electrograms shown in the **top tracing** from the LVAn show a Wenckebach-like conduction pattern. The intracavitary potentials are stable. The Wenckebach-like sequence starts again in the **right** part of the tracing.

of conduction to areas not required to perpetuate VT. A combination of a rate-dependent phenomenon, change in the ventricular activation pattern during VT and Wenkebach-like conduction to areas not required to perpetuate VT has therefore to be considered to explain the observations made in the patient shown in Figure 7.

Pacing-induced change from noncontinuous electrograms into continuous electrical activity without the prevention of termination of VT: In 2 patients during overdrive ventricular pacing, electrograms that were noncontinuous during VT could be changed into continuous electrical activity by rapid ventricular pacing from the right ventricle. However, this did not prevent termination of VT (Fig. 8). This was probably a rate-dependent phenomenon that also depended on the ventricular activation pattern (the QRS being different during pacing as compared to VT) and widening of the electrograms during rapid pacing.

Termination of continuous electrical activity by antiarrhythmic drugs without termination of VT: In 7 patients an antiarrhythmic drug was given intrave-

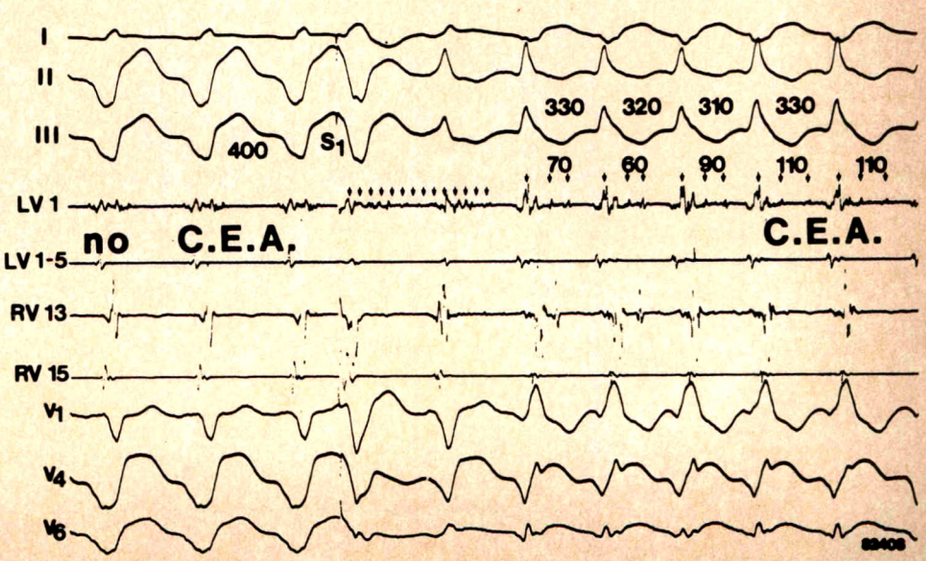

FIGURE 7. Left, a ventricular tachycardia with left bundle branch block morphologic pattern, left-axis deviation, and a cycle length of 400 ms. Continuous electrical activity (C.E.A.) is not observed at the left ventricular (LV) recording site 1 (aneurysm) or site 1–5 (border zone). A single ventricular premature beat (S_1) initiates transient continuous electrical activity at LV1 and results in another ventricular tachycardia with right bundle branch block morphologic pattern, right axis in the frontal plane and a cycle length of 310 to 330 ms. Progressive fragmentation and delay in the electrograms at LV1 are observed, resulting in continuous electrical activity in the last cycles. RV13, RV15 = right ventricular sites.

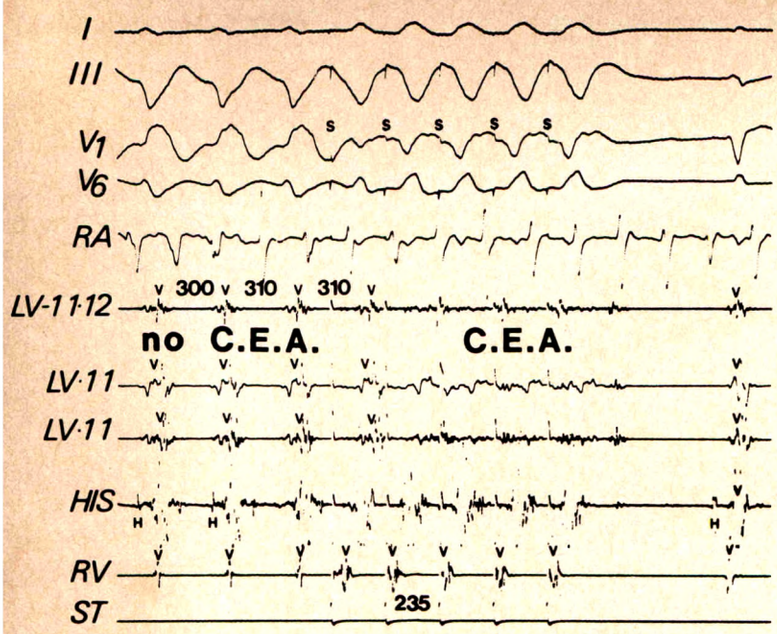

FIGURE 8. Change of noncontinuous electrograms into continuous electrical activity (C.E.A.) by overdrive ventricular pacing during ventricular tachycardia (VT) without preventing termination of VT. **Left,** a VT with a right bundle branch block morphologic pattern, left axis in the frontal plane and a cycle length of 300 to 310 ms. Overdrive ventricular pacing from the right ventricular (RV) apex with a cycle length of 235 ms is done for 5 beats. The electrograms at left ventricular (LV) recording sites 11 and 11–12 change from noncontinuous during VT to continuous electrical activity during overdrive ventricular pacing. These potentials widen and span markedly diastole after the last paced complex. However, initiation of continuous electrical activity did not prevent pacing termination of VT.

nously during VT at the time of recording of continuous electrical activity. Two patients received intravenous amiodarone, 2 procainamide, 1 patient disopyramide, and 2 propafenone. In 3 patients (1 receiving amiodarone, 1 disopyramide and 1 propafenone), continuous electrical activity terminated without reappearing during the slowing in rate of VT (Fig. 9). This was associated with marked changes in the morphologic pattern of the potentials. However, VT continued with the same QRS morphologic pattern and axis. In 1 other patient, continuous electrical activity disappeared and reappeared spontaneously after intravenous procainamide, demonstrating that continuous electrical activity was not essential to perpetuate the arrhythmia.

Relation between the areas showing continuous electrical activity during VT, recordings during sinus rhythm and ventricular anatomy: In all 20 patients who had continuous electrical activity during VT, correlation with the ventricular anatomy revealed that continuous electrical activity was recorded within the aneurysm. No patient showed continuous electrical activity over areas with normal wall motion. Recordings during sinus rhythm over the area that showed continuous electrical activity during VT were invariably abnormal. In all patients, low-amplitude potentials (in 19 patients less than 1 mV) lasting 50 ms or more were recorded. These potentials continued after the end of the QRS complex in the surface leads.

Abnormal potentials during sinus rhythm were not recorded in any patient in the idiopathic-VT group.

Continuous electrical activity was recorded in the coronary sinus in 3 patients. All 3 had an inferoposterior wall MI with a large aneurysm (Fig. 10).

Discussion

In 1978, Josephson et al[17] described the phenomenon of continuous electrical activity during endocavitary left ventricular mapping in patients with sustained, monomorphic VT. In that report and subsequent reports they did not report how often continuous electrical activity could be recorded in these patients. Our study in 56 patients showed the presence of electrical activity bridging 2 consecutive QRS complexes during monomorphic VT in 36% of patients with VT-old MI, 83% of patients with VT-RV dysplasia, and its absence in patients with idiopathic VT. In 17 of 20 patients, study of the dynamic behavior of continuous electrical activity revealed that electrical activity resembling continuous electrical activity was a transient phenomenon or could be terminated without resulting in termination of VT. To our knowledge, this transient form of continuous electrical activity has not been described previously and illustrates the need for careful study of the dynamic behavior of continuous electrical activity before giving it mechanistic significance. The type of continuous electrical activity recorded in our study was not essential to perpetuate VT in 17 of 20 patients. In the remaining 3 patients, continuous electrical activity persisted during VT and could not be terminated. This does not prove, however, that continuous electrical activity was essential to perpetuate the arrhythmia.

Our investigation was directed by the "intention-to-record" continuous electrical activity. Although careful mapping during VT was performed the actual incidence of continuous electrical activity in our 56 patients must be interpreted with caution. The difficulties to reach certain left ventricular areas of the heart by a catheter technique are well known. We believe that the real incidence of continuous electrical activity in patients with VT-old MI is higher than the one we documented. The absence of continuous electrical activity from areas showing normal wall motion in the VT-old MI and VT-RV dysplasia groups strengthens the observations made in the idiopathic-VT

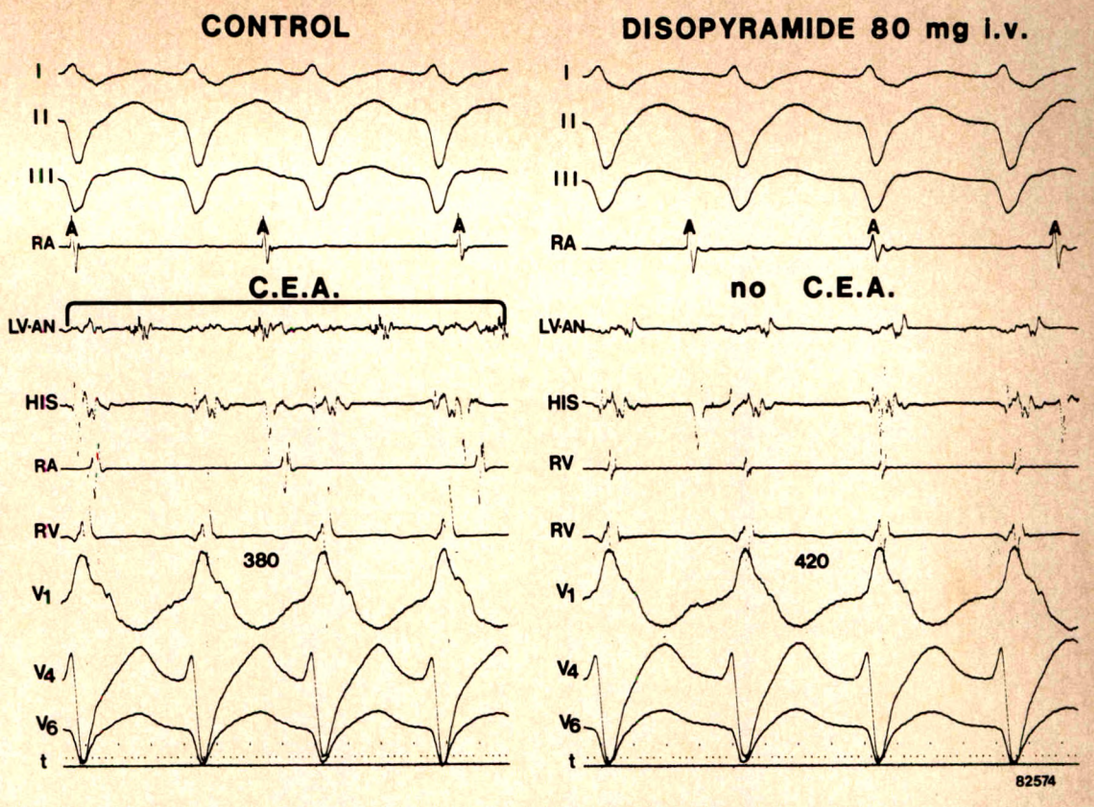

FIGURE 9. Termination of continuous electrical activity (C.E.A.) by intravenous administration of disopyramide without terminating ventricular tachycardia (VT). **Left,** continuous electrical activity at the left ventricular aneurysm (LV-An) during VT with a cycle length of 380 ms. The catheter was stabilized in this position and continuously checked. Disopyramide was given intravenously. The VT cycle length lengthened to 420 ms and a marked change in the morphologic pattern of the potentials recorded occurred, with termination of continuous electrical activity. Disappearance of continuous electrical activity at this recording site did not prevent perpetuation of VT with the same QRS morphologic pattern and axis. Both panels were recorded during the same episode of VT. RA = right atrium.

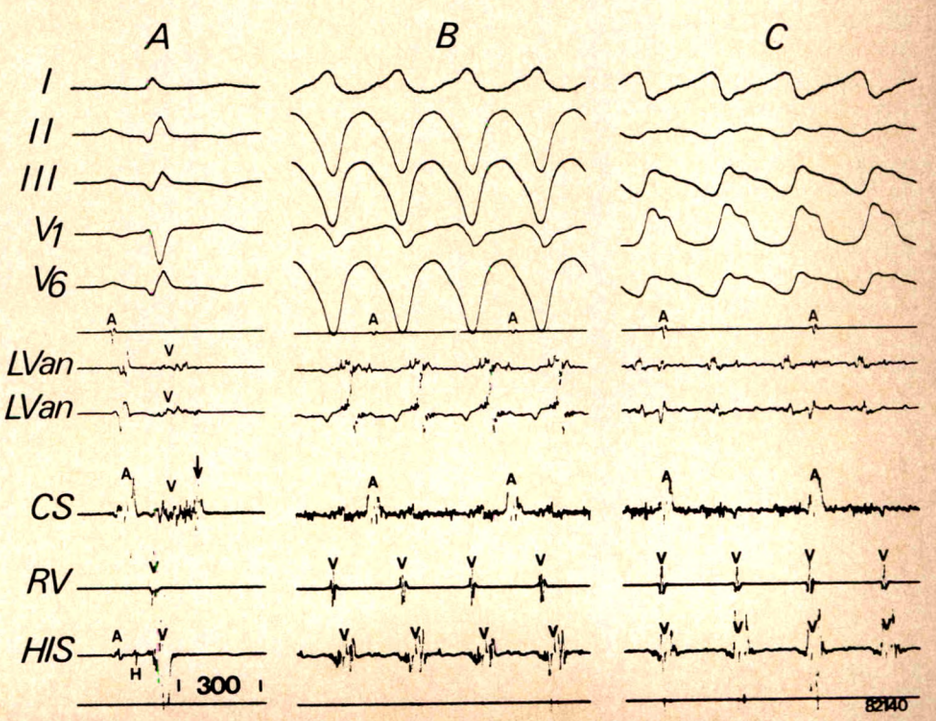

FIGURE 10. An organized pattern of continuous electrical activity is observed during 2 morphologically distinct monomorphic ventricular tachycardias in the coronary sinus (CS) in a patient with an inferoposterior myocardial infarction. **A,** recordings during sinus rhythm show abnormal potentials at the left ventricular aneurysm (LVAn) and at the CS (**arrow**). **B** and **C,** continuous electrical activity is observed during ventricular tachycardia in the CS, and in panel **C** in the LVAn.

group. Continuous electrical activity was not found in any patient from the last group. This may indicate that our recording techniques were not refined enough to record from abnormal areas too small to be identified by angiography, or simply that continuous electrical activity was indeed absent in patients with idiopathic VT and in areas with normal ventricular muscle. Further elucidation of these problems can only be obtained during careful, visually directed mapping of the open heart.

The present study has obvious limitations. Apart from our inability to record from all ventricular areas, catheter mapping is an imprecise method. The amplification and filter settings used in our study may have markedly influenced our results.[18] We did not compare different filter settings and all recordings were bipolar. Only endocardial mapping was performed in these patients. Therefore, we do not know what was occurring at the intramural or epicardial level during VT. Although the electrode catheter was held in the same position, some of our observations could have been the result of slight changes in catheter position. Often, the 2 closely recorded bipolar electrograms showed marked differences. Our only proof for stability in catheter position is the reproducibility of the recorded electrograms. These limitations, however, do not invalidate the observations made on the dynamic behavior of continuous electrical activity, because the filter setting or gain were not changed at the time of recording of these phenomena.

Ideker et al[15] showed that late fractionated potentials and continuous electrical activity can be caused by electrode motion. They stated that "additional evidence should be presented to indicate that the potentials are not caused by motion at the electrode-tissue interface. Such additional evidence could be a change in the late potentials during the beginning or end of an arrhythmia in the absence of a change in heart motion, Mobitz type I or II block in the delayed potentials, or loss of continuous electrical activity with ventricular pacing at the same rate as the tachycardia." We observed that continuous electrical activity could disappear and reappear spontaneously during VT without any change in rate or QRS morphologic pattern during VT. Thus, motion at the electrode-tissue interface as a causal mechanism is very unlikely. Continuous electrical activity could also be terminated by pacing without terminating VT. In some patients with marked spontaneous or pacing-induced variations in rate of VT, continuous electrical activity was a rate-dependent phenomenon present at the initiation of the arrhythmia and after acceleration of tachycardia. Continuous electrical activity also depended on the ventricular activation pattern during VT, and was produced in some patients by Wenckebach-like conduction patterns to areas not required to perpetuate VT. This last observation is similar to that reported by Rosenfeld and Batsford[19] in a patient with RV dysplasia. Continuous electrical activity could be produced by ventricular pacing in areas showing noncontinuous electrograms during VT without preventing the termination of VT. Finally, continuous electrical activity could be terminated by administration of antiarrhythmic drugs without terminating VT which continued at a slower rate with the same QRS morphologic pattern. At least one of the these phenomena were observed in all but 3 patients. The transient disappearance or termination of continuous electrical activity with perpetuation of VT in 17 of our 20 patients indicates that continuous electrical activity was not essential to perpetuate VT.

We did not include in this study patients with ventricular fibrillation or polymorphic VT. The continuous changes in ventricular activation pattern and rate in these arrhythmias would have made it impossible to assess the dynamic behavior of continuous electrical activity.

Continuous electrical activity was recorded only from abnormal areas of the heart where abnormal potentials were observed during sinus rhythm. As with the patients described by Josephson et al,[17] all of our patients with continuous electrical activity showed, during sinus rhythm, potentials that continued after the end of the QRS complex in the area where continuous electrical activity was observed. The reverse was, not true, however. In all patients in the VT-old MI group, late potentials were recorded during sinus rhythm. In only 15 patients was continuous electrical activity recorded during VT.

The hypothesis that continuous electrical activity during VT represents recording from a reentry circuit has been questioned.[7,14,15] Wit et al[7] and Gallagher et al[14] stressed that continuous electrical activity may represent a "bystander" phenomenon recorded from areas with abnormal conduction, but not essential to perpetuate VT. Our observations support this hypothesis in 17 of the 20 patients studied. It can be argued that the continuous electrical activity recorded in our study differs from that observed by other investigators. There is no clear definition of continuous electrical activity. It was by observing the dynamic behavior of continuous electrical activity that its transient nature was recognized. When recording at areas showing continuous electrical activity had been made for only a few beats, or pacing or drugs would not have been used, our observations would have been identical to those of other investigators. Continuous electrical activity was never recorded during sinus rhythm. When VT terminated, continuous electrical activity was no longer present. One might have incorrectly concluded that continuous electrical activity was essential to perpetuate VT.

In conclusion, the recording of continuous electrical activity with a 1-cm interelectrode distance bipolar catheter is a frequent phenomenon during monomorphic VT. Study of the dynamic behavior of continuous electrical activity shows that it represents electrical activity from abnormal heart areas, not necessarily required to perpetuate VT. Detailed studies in the experimental and clinical laboratory are required to assess the significance of the different types of local electrical activity that can be observed during VT in the human heart.

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Arrhythmias Induced During Termination of Supraventricular Tachycardia

BERND WALDECKER, MD, PEDRO BRUGADA, MD, KAREL den DULK, MD, MANFRED ZEHENDER, MD, and HEIN J. J. WELLENS, MD

Pacing is being used frequently for the treatment of drug-resistant, paroxysmal supraventricular tachycardias (SVT). SVT can usually be terminated by pacing, but arrhythmias may be induced which interfere with the safety of antitachycardia pacing. To quantify these pacing-induced arrhythmias, 453 attempts to terminate SVT in 111 patients were analyzed. The patients were 6 to 73 years old (mean 41); 62 were male. Seventy-six patients had SVT using an accessory atrioventricular bypass, and 35 patients had intranodal SVT. Single and then, if required, multiple ventricular and atrial premature beats and overdrive pacing were delivered from the atrium and ventricle. A pacing-induced arrhythmia occurred in 9% of all attempts (34% of patients). Atrial flutter or fibrillation (AF) was the most frequent arrhythmia (in 8% of all attempts and sustained in 75%). Atrial vs ventricular pacing resulted in a 12% vs 2% incidence of AF. AF was unrelated to age, sex, atrial size and SVT type, and was predominantly induced by multiple premature beats. In 6 patients a different SVT and in 2 patients a nonsustained ventricular tachycardia was induced. In 6 patients SVT could only be terminated by initiating another arrhythmia. Thus, AF is frequently induced during attempted pacing termination of SVT. To limit the risk of AF, a single premature beat should preferentially be used to terminate SVT. In 6% of patients, SVT can only be terminated by inducing another arrhythmia. Therefore, careful investigation of the properties of the clinical SVT by programmed electrical stimulation of the heart is mandatory before considering pacing as therapy for these patients. (Am J Cardiol 1985;55:412–417)

Reentrant tachycardia can usually be initiated and terminated by pacing. A premature, artificially induced depolarization delivered to tissue sustaining the circulating impulse can produce a block in impulse conduction and terminate circus movement. After the initial report of Durrer et al[1] of the ability to initiate and terminate reentrant supraventricular tachycardia (SVT) by properly timed atrial (APB) or ventricular premature beats (VPB), antitachycardia pacing was introduced into clinical cardiology as a new method of treating drug-resistant tachycardias. Whereas Lister et al[2] used an external pacemaker to interrupt SVT by overdrive atrial pacing, Ryan et al[3] used an implanted demand pacemaker, which was converted to an asynchronous underdrive pacing mode by placing the magnet over the pacemaker, thereby giving a single VPB to terminate SVT in a patient with the Wolff-Parkinson-White (WPW) syndrome. Subsequently, several implantable pacemaker systems, which can recognize and terminate tachycardia, have been developed. However, even in the first reports[4–8] of antitachycardia pacing, unwanted arrhythmias were already being described as a possible complication of this form of therapy. To assess these pacing-induced arrhythmias, we analyzed arrhythmias that were induced during attempted pacing termination of SVT in patients with circus-movement tachycardia using an accessory atrioventricular bypass tract and in patients with intranodal tachycardia.

From the Department of Cardiology, University of Limburg, Annadal Hospital, Maastricht, The Netherlands. Manuscript received July 9, 1984; revised manuscript received September 25, 1984, accepted September 26, 1984.

Address for reprints: Pedro Brugada, MD, Clinical Electrophysiology Laboratory, Department of Cardiology, University of Limburg, Annadal Hospital, Maastrict, The Netherlands.

Methods

Patients: Data from 111 consecutive patients with documented paroxysmal SVT were retrospectively analyzed. All patients gave informed consent before the electrophysiologic investigation. In all patients sustained SVT was initiated by programmed electrical stimulation. Their clinical data are listed in Table I. The patients represented a general referral group and were studied for diagnostic (palpitations without documented arrhythmia), therapeutic (drug-resistant SVT) or prognostic reasons (WPW syndrome with short bypass tract refractory period). Seventy-six patients had atrioventricular

TABLE I Clinical Data in 111 Patients

SVT Type		No. of Pts	No. of Studies	F:M	Age (yr) (mean)	TCL (ms)	ATT
AVJT, (WPW)	no AAD	39*	39	11:28	6–59 (35)	335 ± 52	134
	with AAD	10	14	4:10	25–60 (40)	414 ± 74	56
AVJT, (CB)	no AAD	26*	26	7:19	6–65 (37)	364 ± 71	93
	with AAD	1	4	2:2	35–62 (39)	372 ± 40	12
INT,	no AAD	33	33	22:11	27–73 (49)	354 ± 61	128
	with AAD	2	6	3:3	23–57 (46)	394 ± 38	30
Total		111	122	49:62	6–73 (41)	363 ± 65	453

* Including 1 patient with coronary heart disease.

AAD = antiarrhythmic therapy; ATT = attempt to terminate supraventricular tachycardia; AVJT = AV junctional tachycardia using an accessory atrioventricular pathway; CB (as opposed to Wolff-Parkinson-White) = concealed atrioventricular accessory pathway, conducting from the ventricle to the atrium solely; F = female; INT = intranodal tachycardia. The site of reentry is confined to the atrioventricular node. M = male; SVT = supraventricular tachycardia; TCL = tachycardia cycle length; WPW (as opposed to CB) = Wolff-Parkinson-White syndrome with an atrioventricular accessory pathway conducting in both directions.

TABLE II Distribution of Pacing-Induced Arrhythmias in Relation to Attempts to Terminate Supraventricular Tachycardia

SVT Type		1 APB	2 APBs	3 APBs	AOP	1 VPB	2 VPBs	VOP	Total
AVJT, (WPW)	no AAD	4/42 (10%)	5/23 (22%)	0/3 (0%)	1/6 (17%)	2/35 (6%)	2/19 (11%)	0/6 (0%)	14/134 (11%)
	with AAD	1/20 (5%)	0/13 (0%)	2/3 (67%)	1/2 (50%)	1/13 (8%)	0/5 (0%)	–/– –	5/56 (9%)
AVJT, (CB)	no AAD	4/29 (14%)	5/13 (38%)	–/– –	0/11 (0%)	0/24 (0%)	0/12 (%)	0/4 (0%)	9/93 (10%)
	with AAD	1/4 (25%)	0/1 (0%)	–/– –	0/2 (0%)	0/4 (0%)	–/– –	0/1 (0%)	1/12 (8%)
INT	no AAD	5/31 (16%)	5/20 (25%)	0/2 (0%)	0/18 (0%)	0/26 (0%)	2/26 (8%)	0/5 (0%)	11/128 (9%)
	with AAD	1/7 (14%)	0/4 (0%)	0/1 (0%)	0/5 (0%)	0/7 (0%)	0/4 (0%)	0/2 (0%)	1/30 (3%)
Total		15/133 (11%)	15/74 (20%)	2/9 (22%)	2/43 (5%)	3/109 (3%)	4/66 (6%)	0/18 (0%)	41/453 (9%)

APB = atrial premature beat; AOP = atrial overdrive pacing; VOP = ventricular overdrive pacing; VPB = ventricular premature beat; – = none; other abbreviations as in Table I.

(AV) junctional SVT using an accessory bypass as 1 limb of the circuit; in 27 of these patients the bypass was concealed. Thirty-five patients had intranodal SVT. Only 2 patients had structural heart disease, both with coronary heart disease. Eleven patients were studied before and during antiarrhythmic drug treatment (amiodarone in 1, encainide in 2, sotalol in 4, propafenone in 3 and disopyramide in 1). Thirteen patients were investigated only while receiving antiarrhythmic drugs orally (amiodarone in 9, encainide in 3 and lorcainide in 1). Our previously described method of stimulation and recording was used.[9] Electrode catheters were placed at the right atrium, coronary sinus, His bundle area and right ventricular apex. During sustained SVT, premature beats and overdrive pacing were attempted from the atrium and ventricle. Each pacing method was considered as a separate attempt to terminate SVT in an individual patient, however, repetition of the same pacing method was considered as 1 attempt. Four hundred fifty-three attempts to terminate SVT were performed in these 111 patients (mean 4 attempts per study) (122 studies in 111 patients). Single late APBs or VPBs were delivered first, scanning the tachycardia cycle in 10-ms decrements. The premature beat was given after every 6 to 8 tachycardia beats until SVT was terminated, the paced tissue was refractory, or another arrhythmia occurred. Only if a single premature beat at the particular stimulation site failed to terminate SVT and did not initiate an arrhythmia was a second or, if required, a third APB or VPB given. Twenty-beat bursts of overdrive pacing were begun at a rate 10 beats faster than the tachycardia rate, and the pacing rate increased by 5 to 10 beats/min until SVT was interrupted or another arrhythmia initiated. A particular attempt was considered successful only if it never failed to terminate SVT and never initiated another arrhythmia.

The current strength was twice diastolic threshold and the stimulus duration 2 ms. Stimulation was always bipolar.

The size of the left atrium was measured echocardiographically in accordance with the recommendations of the American Society of Echocardiography.[10]

Results

The mean SVT cycle length for the whole group of patients was 365 ms (range 250 to 540). In 34% of all patients (38 of 111) or in 9% of all 453 attempts to terminate SVT, an arrhythmia was induced. The distribution of pacing-induced arrhythmias within the different groups of patients and attempts is shown in Table II. The most frequent pacing-induced arrhythmia was atrial fibrillation or atrial flutter (AF), which occurred in 8% of all attempts and in 30% of patients (Fig. 1). During attempts to terminate SVT by atrial pacing the incidence of AF was 12%, vs 2% during ventricular pacing. Increasing numbers of premature beats raised the risk of AF from 11% (1 APB) to 18% (2 APBs) to 22% (3 APBs) during atrial stimulation and from 1% (1 VPB) to 5% (2 VPBs) during ventricular stimulation (Fig. 2). AF occurred during overdrive pacing from the atrium in 5% of the attempts (2 of 43), but never after ventricular overdrive pacing (18 attempts). There was no difference in the incidence of AF in patients with concealed accessory bypasses compared with patients with the

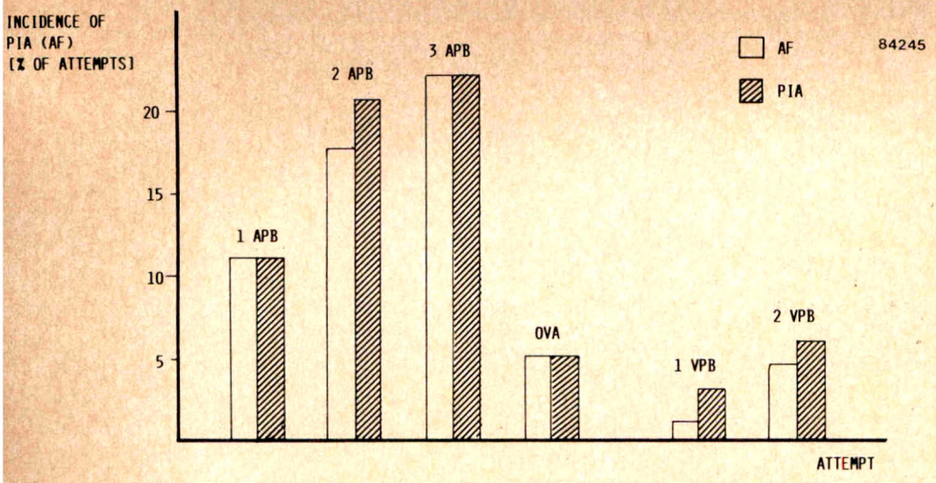

FIGURE 1. Incidence of all pacing-induced arrhythmias (PIA) and of atrial fibrillation/flutter (AF) according to the mode of attempted termination and in relation to the number of attempts performed. Ventricular overdrive pacing never resulted in a pacing-induced arrhythmia and is not illustrated. APB/VPB = atrial/ventricular premature beats; OVA = atrial overdriving.

WPW syndrome, or in all patients with bypasses compared with patients with intranodal SVT ($p > 0.05$). There was no relation between either risk of AF and patient age ($p > 0.05$) or gender ($p > 0.05$). If the cycle length of the SVT was longer than 340 ms, induction of AF was a significantly less frequent event ($p < 0.05$). This was not the result of easier termination of slower SVT by fewer premature beats ($p > 0.05$). The incidence of pacing-induced AF did not differ significantly between untreated patients and patients treated with antiarrhythmic drugs (8.5 vs 5%, $p > 0.05$). AF was sustained (lasting longer than 30 seconds) in 75% of episodes. Injection of an antiarrhythmic drug terminated AF in 2 patients, and successful atrial overdrive pacing of flutter was performed in 5 patients; the study was interrupted 3 times, and in 3 patients, including 1 with WPW syndrome and a rapid ventricular response, AF was cardioverted. The remaining self-terminating episodes of AF lasted for a mean of 5 minutes (range 35 seconds to 20 minutes). Untreated patients with the WPW syndrome had the shortest RR intervals during AF, ranging from 400 to 175 ms; half (8 of 15) had the shortest RR intervals (shorter than 270 ms [220 beats/min]) and 3 of 15 had the shortest RR intervals (shorter than 200 ms [300 beats/min]). Only 3 patients with the WPW syndrome had AF in the presence of antiarrhythmic drugs; their shortest RR intervals were 270, 300 and 350 ms. Spontaneous AF was documented or suspected in 21 patients, but AF was not induced more frequently in them than in the rest of the group ($p > 0.05$). Resumption of the previous SVT after spontaneous termination of AF was seen in 5 patients.

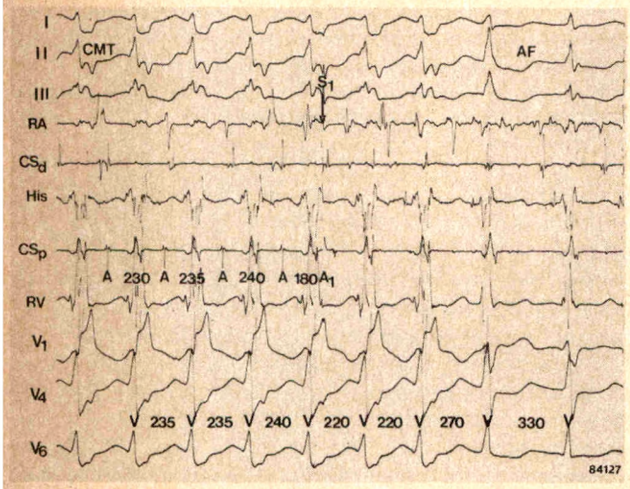

FIGURE 2. Initiation of atrial fibrillation/flutter (AF). During atrioventricular junctional supraventricular tachycardia using a right-sided accessory bypass retrogradely (labeled CMT) with a mean cycle length of 235 ms, an atrial premature beat (A_1) delivered in the high right atrium (RA) induces AF. Atrioventricular conduction predominantly through the atrioventricular node, shortest RR interval, 220 ms. A = atrial deflection; CMT = atrioventricular junctional supraventricular tachycardia; CS_d, CS_p, His, RA, RV = intracardiac recordings from the distal and proximal coronary sinus, His bundle area, high right atrium and right ventricle, respectively; H = His bundle deflection; S = stimulus artifact; V = ventricular complex.

M-mode echocardiograms were available in 66 patients. Left atrial enlargement was present in 8 (12%). The largest atrial size was 48 mm; the maximal left atrial/aortic root ratio was 1.41. The occurrence of pacing-induced AF and left atrial size was unrelated ($p > 0.05$).

In 2 untreated patients, 1 of them with AV junctional SVT using a left-sided accessory bypass, the other with intranodal SVT, a nonsustained ventricular tachycardia (shorter than 30 seconds) developed after 1 and 2 VPBs during SVT, respectively. The first patient, an otherwise healthy 40-year-old man, had 9 beats of polymorphic ventricular tachycardia followed by a monomorphic tachycardia that lasted 11 seconds (Fig. 3). The second patient had a run of nonsustained polymorphic ventricular tachycardia (10 beats).

In 2 patients, 2 APBs changed antidromic into orthodromic AV junctional SVT and was sustained in 1. In 3 other patients with AV junctional SVT during use of an accessory bypass who had dual AV nodal pathways, intranodal SVT was induced by advancing atrial activation either directly by an APB or by retrograde conduction over the accessory bypass following a VPB. Earlier atrial activation found the fast AV nodal pathway refractory, allowing anterograde conduction

solely over the slow AV nodal pathway initiating intranodal SVT. In 1 patient, an APB as well as a VPB during AV junctional SVT induced intranodal SVT (Fig. 4). In 2 of these 3 patients, the induced intranodal SVT was sustained. In another patient with AV junctional SVT, atrial overdrive pacing initiated a sustained atrial tachycardia, which had been clinically documented. In 7 of 111 patients (6%), SVT could be terminated only by initiating another arrhythmia. In these patients all attempted pacing modalities either did not interrupt the SVT or resulted in an arrhythmia; the arrhythmia was AF in 6 patients and intranodal SVT in 1. However, in most patients in whom a pacing-induced arrhythmia occurred, a pacing mode could be found that terminated SVT without initiating a subsequent arrhythmia.

Discussion

Antitachycardia pacemakers have undergone important refinements to obtain greater versatility in recognizing and terminating SVT automatically or by patient-activated system.[11] Termination should be achieved as quickly and as safely as possible. Pacing-induced arrhythmias are an undesirable complication of the electrical treatment of paroxysmal SVT.[5,6,12–14] Antitachycardia pacemakers use 1 or several of the following pacing modalities to terminate SVT: (1) Single extrastimuli with either a fixed coupling interval or scanning the tachycardia cycle to find a zone of termination; scanning can be random, such as underdrive pacing, or the coupling interval can be changed by a predetermined interval. (2) Scanning with 2 or more extrastimuli. (3) Increasing number of extrastimuli at fixed or adaptive intervals until SVT is interrupted. (4) Overdrive pacing with fixed, adaptive or variable intervals between the trains of stimuli.[15]

Whenever pacing is performed, however, nonclinical arrhythmias can be initiated. We observed that during attempted pacing termination of SVT, AF was the most common pacing-induced arrhythmia. As expected, atrial stimulation yielded a considerably higher incidence of AF than stimulation in the right ventricular apex, but ventricular stimulation during SVT still resulted in a 2% incidence of AF. Regardless of the stimulation site, the risk of AF increased with the number of premature beats. Initiation of AF during ventricular stimulation in 3 patients was the result of rapid retrograde VA conduction over an accessory bypass tract resulting in premature atrial stimulation. In 1 patient, 2 VPBs during intranodal SVT induced AF. However, in this patient, an accessory bypass not participating in the SVT could not be definitely excluded. The incidence of AF during SVT may have been higher if multiple APBs had been given systematically to each patient. Although multiple APBs were given frequently, for the purpose of this study they were analyzed only if a single APB failed to terminate SVT and did not result in another arrhythmia. We did not observe a significant difference in the incidence of AF in patients with AV junctional SVT and in patients with intranodal SVT, although it has been suggested that enhanced atrial vulnerability exists in patients with the WPW syndrome.[16]

Atrial overdrive pacing was not as prone to induce AF as suggested by other studies. We found an incidence of 5%, which is much lower than the 17.5% incidence reported by other investigators.[13] Two variations in population and pacing modes may have accounted for these differences. First, overdrive pacing was attempted during SVT after giving premature beats. Second, our initial pacing cycle length was only 5 to 10 ms shorter than the tachycardia cycle length and was shortened in steps of 5 to 10 beats/min until termination of SVT.

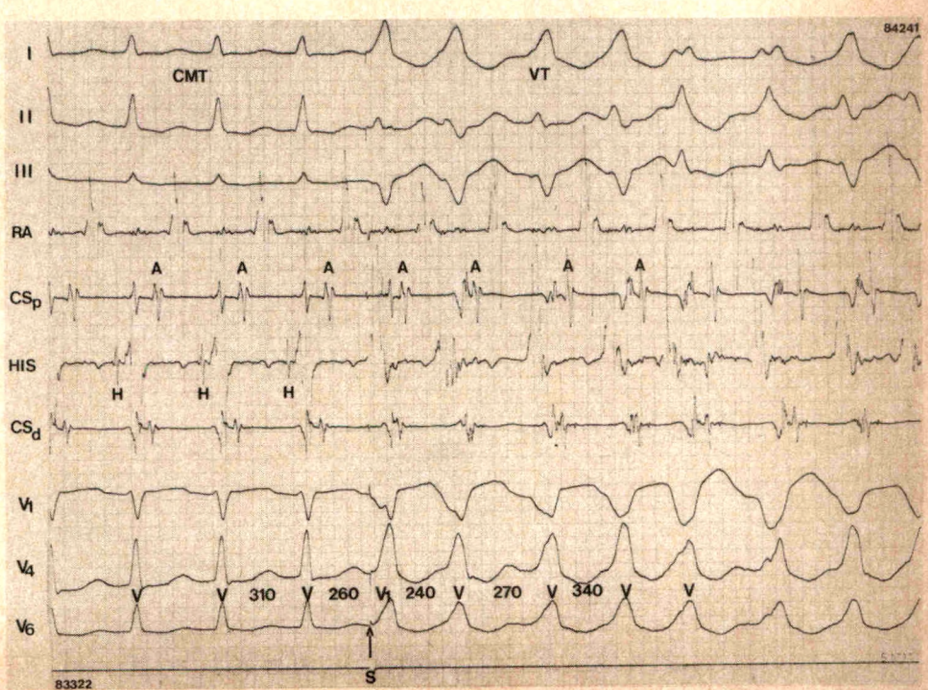

FIGURE 3. Induction of nonsustained ventricular tachycardia (VT). A ventricular premature beat (V_1) given in the right ventricular apex during atrioventricular junctional tachycardia (labeled CMT) using a left-sided accessory bypass induces (nonsustained) polymorphic VT. Abbreviations as in Figure 2.

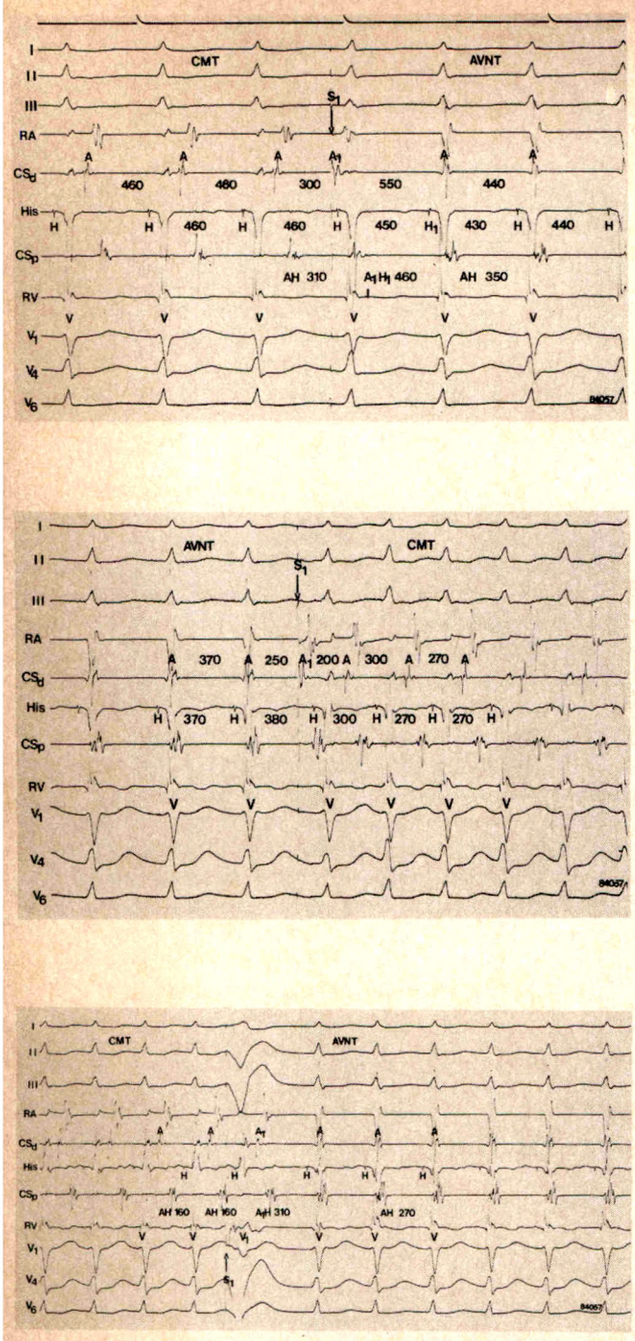

FIGURE 4. Inability to terminate supraventricular tachycardia (SVT) by premature beats from the atrium (**top** and **middle**) and the ventricle (**bottom**) in a patient with an accessory atrioventricular (AV) bypass and dual AV nodal pathways. Atrial flutter/fibrillation was also initiated in this patient by rapid atrial pacing. **Top,** 1 atrial premature beat (S_1) given in the distal coronary sinus (CS_d) during AV junctional SVT renders the atrium refractory for the subsequent retrograde activation over the accessory bypass, enters the slow AV nodal pathway, allowing the fast pathway to recover, and thereby initiates intranodal SVT. **Middle,** 1 atrial premature beat (S_1) given in the CS_d during intranodal SVT collides within the fast AV nodal pathway, blocks anterogradely in the slow AV nodal pathway and allows resumption of AV junctional SVT. **Bottom,** 1 ventricular premature beat during AV junctional SVT advances atrial activation over the accessory bypass and penetrates the fast AV nodal pathway retrogradely. Subsequent ventricular activation occurs over the slow AV nodal pathway and initiates intranodal SVT. Abbreviations as in Figure 2.

This may be less likely to initiate AF than overdrive pacing at a faster initial pacing rate.

Pacing during tachycardias faster than 175 beats/min resulted in a higher incidence of AF than pacing during tachycardias slower than 175 beats/min. This difference in the incidence of AF was not the result of termination of slower SVT by fewer extrastimuli.

During pacing-induced AF, we observed short RR intervals due to rapid AV conduction over the accessory bypass in patients with the WPW syndrome, but we did not observe collapse or initiation of ventricular fibrillation in any of these patients as previously reported.[17–20] However, reinitiation of AV junctional SVT was observed in 5 patients when pacing-induced AF terminated spontaneously.[16]

In 3 patients, AV junctional SVT was exchanged for intranodal SVT during attempted pacing termination. This could occur because of the presence of dual AV nodal pathways. We found dual AV nodal pathways in 18 of 76 patients (24%) with an accessory bypass. Although only 3 of these 18 patients also had intranodal SVT induced during attempted termination, in 1 patient AV junctional SVT was repeatedly changed into sustained intranodal SVT by APB and VPB and could not be reproducibly terminated by pacing.

APB changed antidromic AV junctional SVT into orthodromic SVT in 2 patients and nonsustained ventricular tachycardia was induced by VPB in another 2 subjects; in all 4, however, an effective and safe mode of pacing termination was subsequently found.

In 66 of 111 patients in whom echocardiograms were available, left atrial size was normal and unrelated to the incidence of AF.

Although we observed a pacing-induced arrhythmia due to attempted termination of SVT in 34% of patients, in most of them an alternative, safe and reliable mode of interruption of SVT by pacing was found. Of this series of 111 consecutive patients, SVT could not be terminated by APBs, VPBs or overdrive pacing in 7 patients (6%) without initiating another arrhythmia, which was AF in 6. Antitachycardia pacing should not be considered for these patients.

Our results concerning pacing-induced arrhythmias were obtained during electrophysiologic investigation in the catheterization laboratory. Comparison between our findings and clinical antitachycardia pacing with implantable pacemakers is not established, and a strict correlation should be assumed only with caution. For instance, our group represents a general referral group. The incidence of pacing-induced arrhythmias may have been underestimated due to easier termination of SVT in these patients than in patients with drug-resistant SVT. Drug-resistant SVT may be faster or more difficult to terminate, thus increasing the likelihood of inducing another arrhythmia.

We conclude that attempted termination of SVT by pacing results in initiation of another arrhythmia in up to 34% of patients. Of these, AF is the most common and occurs in up to 30% of patients and is sustained in 75%. Ventricular stimulation during SVT can induce nonsustained ventricular tachycardia. Careful evaluation

of the nature and consequences of these arrhythmias, particularly in patients with the WPW syndrome and a short anterograde refractory period of the accessory pathway, is mandatory before instituting ATP for the treatment of paroxysmal SVT. In most of these patients, however, a pacing mode can be found that will reliably and safely terminate SVT. In 6% of the patients, the tachycardia can be terminated only by initiating another arrhythmia. These patients are not candidates for antitachycardia pacing.

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Maximal Hand Blood Flow in Hypertensive and Normal Subjects

DAVID HORWITZ, MD, and DALI J. PATEL, MD, PhD

The present study examined whether patients with systemic hypertension have evidence of structural vascular changes, whether such changes can be detected in early stages of hypertension and whether they are reversible with treatment. Hypertensive and normal subjects were studied under conditions of maximal vasodilation in which flow at a given driving pressure was considered to give an index of structural changes in resistance vessels. Thirty-two subjects were separated into 4 groups: 8 with sustained hypertension, 8 with intermittent hypertension, 8 treated hypertensive subjects maintained at systolic pressures of less than 125 mm Hg with drugs for 5 years, and 8 normal subjects. Flow was measured by venous occlusion plethysmography after 10 minutes of ischemia, using a water-filled plethysmograph at 43°C. Arterial blood pressure was measured by the arm cuff method. Transmural pressure, calculated as mean arterial minus external pressure, was varied by imposing varying external hydrostatic pressures. Flow at a transmural pressure of 85 mm Hg was calculated for each subject from the least-mean-square plot of transmural pressure vs flow. Mean flow for normal subjects was 41 ml/100 ml/min and differed significantly from that for sustained hypertensive patients (30 ml/100 ml/min), treated hypertensive patients (33 ml/100 ml/min), and intermittent hypertensive patients (32 ml/100 ml/min) ($p < 0.05$). There was no overlap between sustained hypertensives and normal subjects, but half of the treated hypertensive patients were normal. Intermittent hypertensive patients usually showed evidence of pronounced arterial changes. Prolonged therapy appeared to reverse changes in some sustained hypertensives. This noninvasive method permits comparisons of hypertensive and normotensive subjects at equivalent transmural pressures.

(Am J Cardiol 1985;55:418–422)

Essential systemic hypertension in humans and spontaneous hypertension in the rat are characteristically associated with increased peripheral resistance.[1–3] This in turn may result from changes in smooth muscle tone or from structural changes in small blood vessels. The present study is concerned with whether hypertensive subjects show evidence of structural vascular changes when compared at equal transmural pressures, whether such changes can be detected in early stages of hypertension and whether they are reversible with treatment. Hypertensive and normal subjects were studied under conditions of maximal vasodilation wherein flow at a given driving pressure was considered to give an index of structural changes in resistant vessels.

From the Hypertension-Endocrine Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and the Department of Physiology and Biophysics, College of Medicine, Howard University, Washington, D.C. Manuscript received June 29, 1984; revised manuscript received October 30, 1984, accepted October 31, 1984.

Address for reprints: Dali J. Patel, MD, PhD, Department of Physiology and Biophysics, College of Medicine, Howard University, Washington, D.C. 20059.

Methods

Subjects: The subjects were 24 patients with uncomplicated sustained or intermittent essential hypertension and 9 normal subjects. The subjects were separated into 4 groups:

Group I (sustained hypertensives): Each subject showed blood pressure (BP) readings of at least 140/90 mm Hg in supine and erect postures on each visit. Six subjects were untreated and 2 were hypertensive despite treatment.

Group II (intermittent hypertensives): Subjects were untreated and showed BP levels that varied above and below 140/90 mm Hg.

Group III (optimally treated hypertensives): Before treatment, each subject had shown sustained hypertension during 4 to 6 visits (average BP for all subjects 155 ± 7/101 ± 4 mm Hg supine, and 156 ± 5/109 ± 3 mm Hg standing). Thereafter, each subject showed systolic BP readings that did not exceed 125 mm Hg on all visits during at least 5 years of treatment before study (average of 118 ± 2/80 ± 2 mm Hg supine, and 118 ± 1/86 ± 1 mm Hg standing).

Group IV (normal subjects): Each showed BP levels less than 125/80 mm Hg in supine and standing positions during each visit.

TABLE I Patient Characteristics

	Sustained Hypertensives Group I	Intermittent Hypertensives Group II	Treated Hypertensives Group III	Normal Subjects Group IV
BP (mm Hg)*				
Supine	154 ± 3/101 ± 3	138 ± 3/87 ± 2	118 ± 2/80 ± 2	110 ± 3/66 ± 2
Standing	156 ± 4/108 ± 2	134 ± 2/97 ± 2	108 ± 1/86 ± 1	108 ± 2/75 ± 1
Age (yr)	43 (33–52)	45 (28–54)	49 (37–61)	41 (27–50)
Race	6B/2W	4B/4W	3B/5W	2B/6W
Sex	3F/5M	2F/6M	2F/6M	2F/6M

* Average of 6 visits for groups I, II and IV and of all visits during at least 5 years for group III. Blood pressures (BP) before initiation of therapy in group III averaged 155 ± 7/101 ± 4 (supine) and 156 ± 5/109 ± 3 (standing) during 4 to 6 visits. BP values are mean ± standard error of the mean; age values are mean and range (years).

Assignments to various groups were based on BP recordings during 6 different visits over 4 to 6 weeks preceding experimental studies for groups I, II and IV and all BP recordings (at least 12 per subject) during at least 5 previous years of continual observations for group III. Patient characteristics and BP for each group before entering the study are shown in Table I. The various groups were reasonably matched, though not exactly, for age and sex. All subjects received no medication for at least a week before plethysmography.

Procedures: Studies were performed in a room maintained at a temperature of 22 to 26°C. BP was measured in 1 arm with a sphygmomanometer. Hand blood flow was measured in the other arm by venous occlusion plethysmography immediately after 10 minutes of arterial occlusion intended to produce maximal vasodilation. A water-filled plethysmograph was used as shown in Figure 1. The hand was enclosed in a loosely fitting thin rubber glove and placed in a rigid chamber, and maintained above heart level in all studies. The chamber was filled from a constant temperature bath maintained at 43°C; water in the chamber was exchanged with that in the bath for 3 minutes before each run. The plethysmograph chamber was connected by Tygon® tubing to a cylinder containing a float that displaced a linear motion transducer as the water level rose. The linear displacement was calibrated to measure volume changes by injecting known amounts of water into the chamber. The cylinder was placed on a platform that was raised or lowered on a pole to give varying levels of hydrostatic pressure in the chamber.

Before each run the veins of the hand were emptied by elevating the pressure in the chamber. Thereafter, the cuff on the forearm was abruptly filled with air and maintained at suprasystolic levels for 10 minutes to induce ischemia (Fig. 2). Flow during postischemic vasodilation was measured after

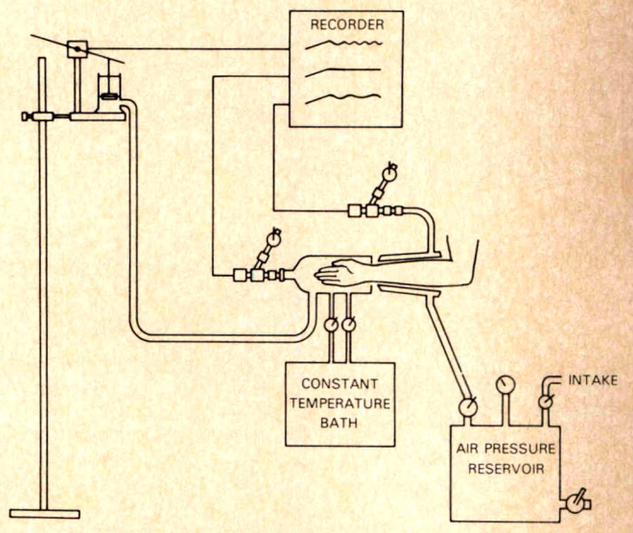

FIGURE 1. The experimental apparatus.

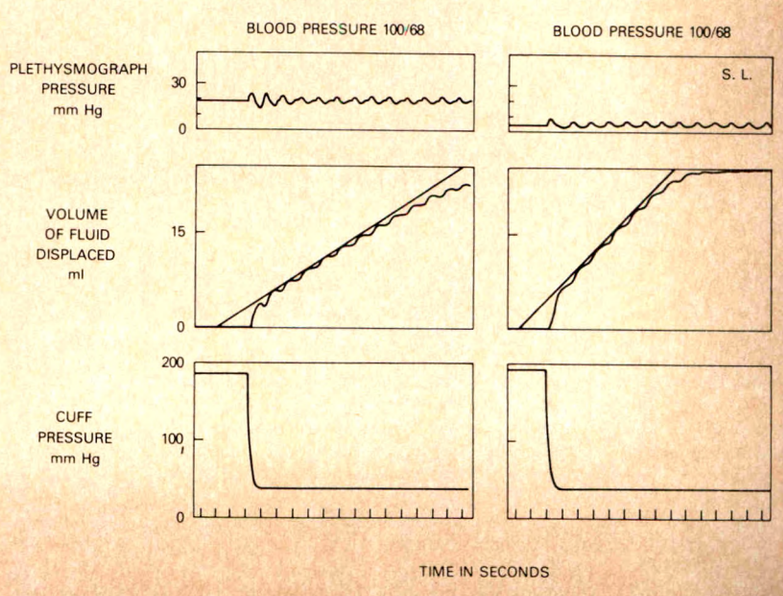

FIGURE 2. Curves of displacement of fluid from the plethysmograph after abrupt reduction of cuff pressure from occlusive levels. Studies are of the same subject (S.L.) at 2 plethysmograph pressures. The more rapid displacement of fluid with a lower external pressure in the plethysmograph reflected the greater hand flow accompanying a higher transmural pressure.

abruptly reducing the cuff pressure to between 40 and 60 mm Hg, which was higher than the chamber pressure but lower than the diastolic BP. Under these circumstances, the arterial inflow to the hand resumed in the absence of venous outflow, resulting in an increase in the volume of the hand. This in turn displaced fluid from the chamber. Hand blood flow (ml/s) was measured from the initial slope of the curve of volume displacement vs time. Such measurements were based on a line drawn tangent to 3 complexes (excluding the first complex which often included a cuff artifact) as shown in Figure 2.

In a typical study, the subjects underwent 6 to 8 runs separated by intervals of 3 minutes, during which the temperature in the chamber was equilibrated with the constant temperature bath. A series of different levels of chamber pressure (5 to 40 mm Hg) was imposed on the hand by varying the height of the meniscus in the cylinder above the chamber (Fig. 2). Chamber pressure and cuff pressure were recorded continuously by Statham gauges (P23Db). Measurements and decisions about suitability of runs were made by an observer blinded to the clinical status of the subject.

Blood flow increased in successive postischemic runs and stabilized by the third run. Because of this, the first 2 runs of a series of 6 to 8 runs were discarded and a curve of flow vs transmural pressure was computed for each subject using a least-mean-square plot of the remaining runs. The predicted flow for a transmural pressure of 85 mm Hg was obtained from this curve for each subject.

An additional normal subject underwent studies to determine whether flow during postischemic vasodilation was altered by the reflex sympathetic discharge resulting from placing the contralateral hand in ice water for up to 3 minutes. The findings are shown in Figure 3. Flow during the hyperemic state was unchanged when the contralateral hand was placed in ice water and followed the linear relation of flow vs transmural pressure observed when the contralateral hand was at 25°C. In the absence of hyperemia, flow decreased markedly after immersion of the contralateral hand in ice water, despite increased BP.

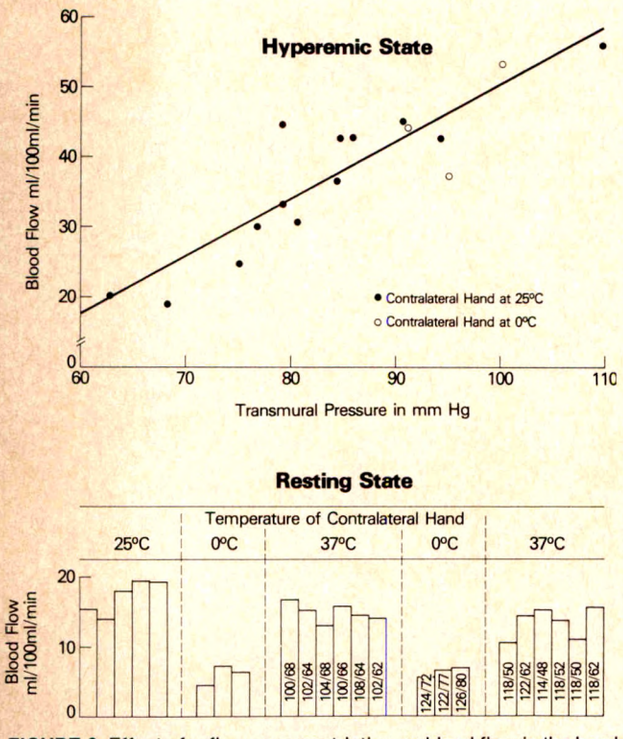

FIGURE 3. Effect of reflex vasoconstriction on blood flow in the hand during and in the absence of postischemic hyperemia. **Top,** during the hyperemic state the relation of blood flow and the transmural pressure was similar when the contralateral hand was at room temperature (**solid circles**) and when it was immersed in ice water (**open circles**). **Bottom,** in the absence of postischemic hyperemia, blood flow decreased strikingly in response to immersing the contralateral hand in ice water despite higher systemic blood pressures.

Theoretical considerations and data analysis: The hemodynamics of blood vessels subjected to external pressure is governed by the Starling resistor, or waterfall, phenomenon[4] provided that the external pressure (P_θ) lies between inflow pressure (P) and the outflow pressure (P_0). In this model, flow (Q) is independent of the exit pressure. Flow is then governed by the driving pressure, which in this case is equal to the transmural pressure, i.e., inflow pressure (P) minus external pressure (P_θ) and is not influenced by variations of P_0.[4,5]

In this study, the mean value of the lumen pressure (P) at the arterial end was determined using a sphygomanometer on the opposite arm and calculated as P = diastolic blood pressure + 1/3 pulse pressure. With the hand in the plethysmograph chamber, P_θ was considered to be the chamber pressure as measured by a Statham gauge. P_0, the pressure in the veins outside of the chamber, was not measured; however, it was assumed to be low in the initial filling phase.

The transmural pressure at the arterial end was calculated as[6]:

$$TMP = P - P_\theta.$$

The resistance (R) of the vascular bed within the chamber is given as:

$$R \simeq \frac{P - P_\theta}{Q} \simeq \frac{TMP}{Q}.$$

In Figure 4, flow is plotted against transmural pressure. The slope of this curve gives the reciprocal of resistance (i.e., conductance) of the vascular bed of the hand.

Results

Figure 4 is a plot of hand blood flow vs transmural pressure of individual runs of normal subjects (Group IV) and patients with sustained hypertension (Group I). The regression lines for each group differed significantly in position ($p < 0.001$), but not in slope ($p < 0.2$). The flow increased with an increase in transmural pressure in both groups but at a given value of transmural pressure, flow was higher in the normal subjects.

Figure 5 shows the hand blood flow at 85 mm Hg transmural pressure for each subject. The mean and standard error of the mean for each group are also shown. Flow in this case is inversely proportional to vascular resistance because the driving pressure, equal to transmural pressure, is constant. Mean flow of normal subjects differed significantly from mean flow of each of the hypertensive groups ($p < 0.05$) when analyzed by analysis of variance. Analysis by a nonparametric method (Kruskal-Wallis statistic with Miller approximation) similarly showed a significant difference between normal subjects and patients with sustained or intermittant hypertension ($p < 0.05$), but significance was not achieved for the comparison of normal subjects and treated hypertensive patients.

Values of computed flow for individual untreated sustained hypertensive patients did not overlap values

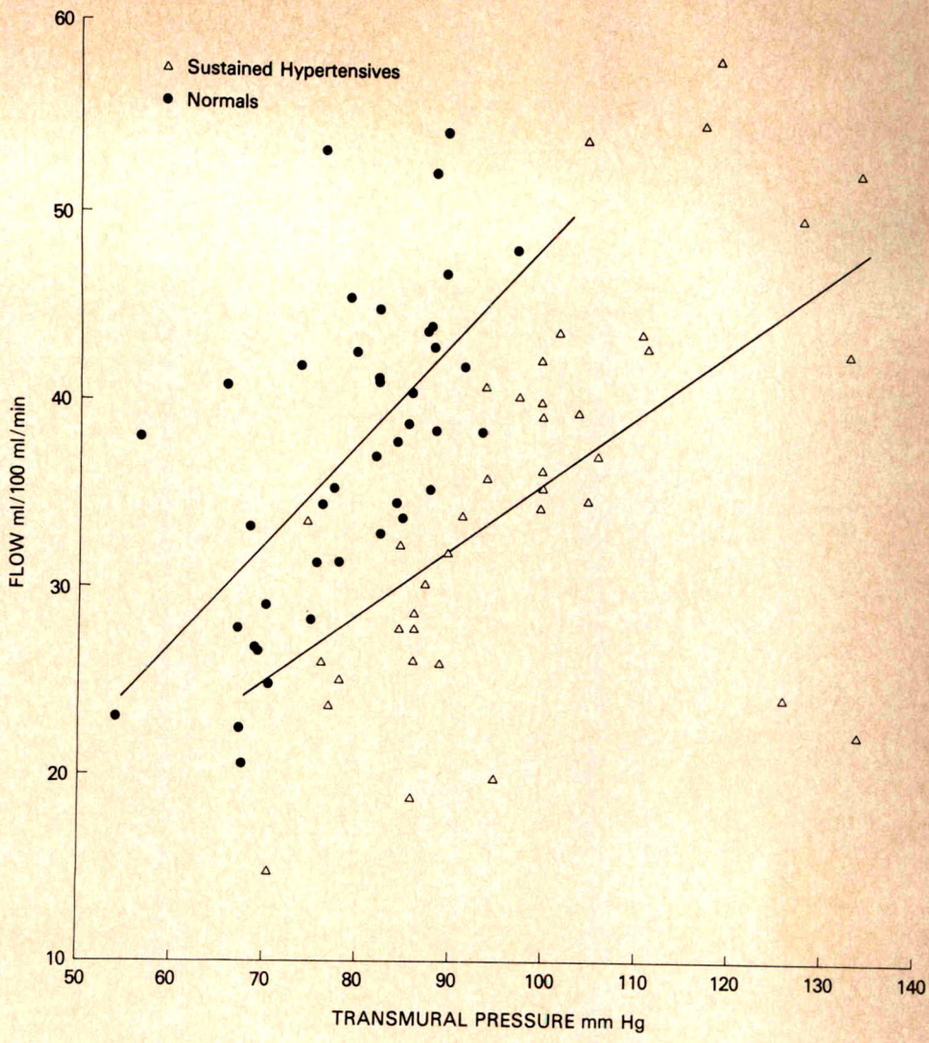

FIGURE 4. Relation of hand blood flow and transmural pressure during all studies of untreated sustained hypertensives and normal subjects. Regression lines are plotted for the 2 groups.

for normal subjects, whereas half of treated hypertensive patients resembled normal subjects. Analysis by Fisher's exact test showed significant differences between the treated and sustained hypertensive groups ($p < 0.03$). There was no obvious relation between the types of drugs received (diuretics, propranolol, methyldopa or hydralazine) and failure of flow to reach control levels.

The only intermittent hypertensive patient with high hand blood flow in Figure 5 clinically appeared to have a hyperdynamic circulation with tachycardia.

Discussion

The present study shows that hand blood flow and vascular conductance of hypertensive subjects during postischemic vasodilation was less than that of normal subjects. Similar results have been obtained by others in the forearm[1,3] and hand.[7]

Based on observations of others using infusions of norepinephrine[1,3] or phenylephrine[8] or using sym-

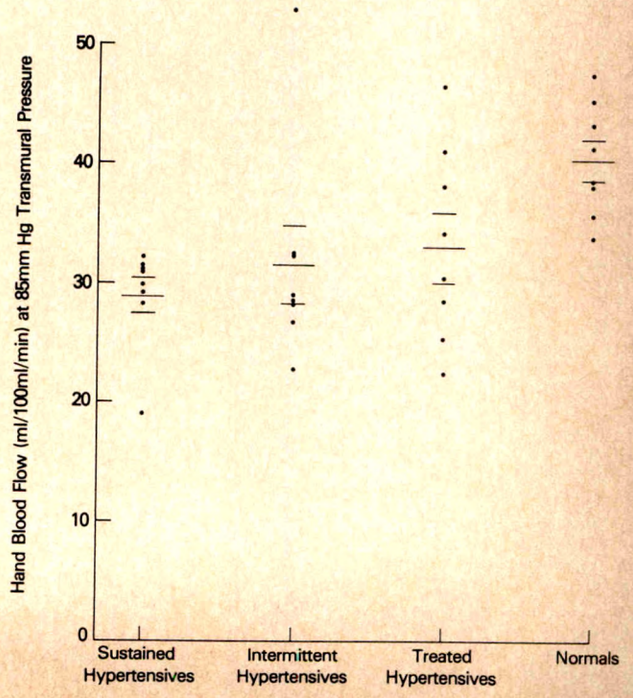

FIGURE 5. Computed hand blood flow at a transmural pressure of 85 mm Hg for each subject in the 4 groups. Mean flow and standard error of the mean for each group are also plotted.

pathectomized subjects,[9] it is reasonable to assume that the postischemic blood flow during maximal vasodilation is relatively free from the influence of sympathetic nervous tone. In the present study we could not evoke reflex vasoconstrictive responses to a cold stimulus during postischemic vasodilation, whereas pronounced responses occurred during control observations in the same subject (Fig. 3).

Assuming an absence of sympathetic neurohumoral or other vasoconstrictor influences during postischemic vasodilation, the caliber of the blood vessel would be governed by the transmural pressure of the vessel and structural changes in the vessel wall. Since comparisons between various groups were made at comparable values of transmural pressure,[6] the results of the present study, i.e., a decrease in hand blood flow and an increase in vascular resistance in hypertensive subjects (Fig. 4 and 5), suggest structural changes in the small blood vessels of the hand. Our findings in the treated hypertensive patients suggest that such structural changes may be reversed by prolonged therapy. Similar results were obtained by Sivertsson and Hanson[10] in patients restudied after 5 years of therapy.

The method was sensitive enough to pick up early changes in blood vessels of intermittent hypertensives. Similarly, Takeshita et al[8,11] showed a lower vasodilator capacity of forearm resistance vessels in borderline hypertensive patients and normotensive subjects with a family history of hypertension. Thus, this simple noninvasive method may be useful in following the adaptation of blood vessels in the early states of hypertension and during various therapies.

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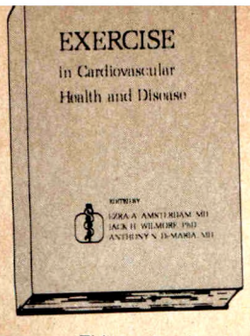

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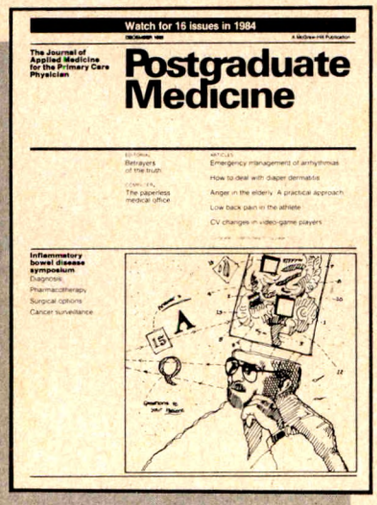

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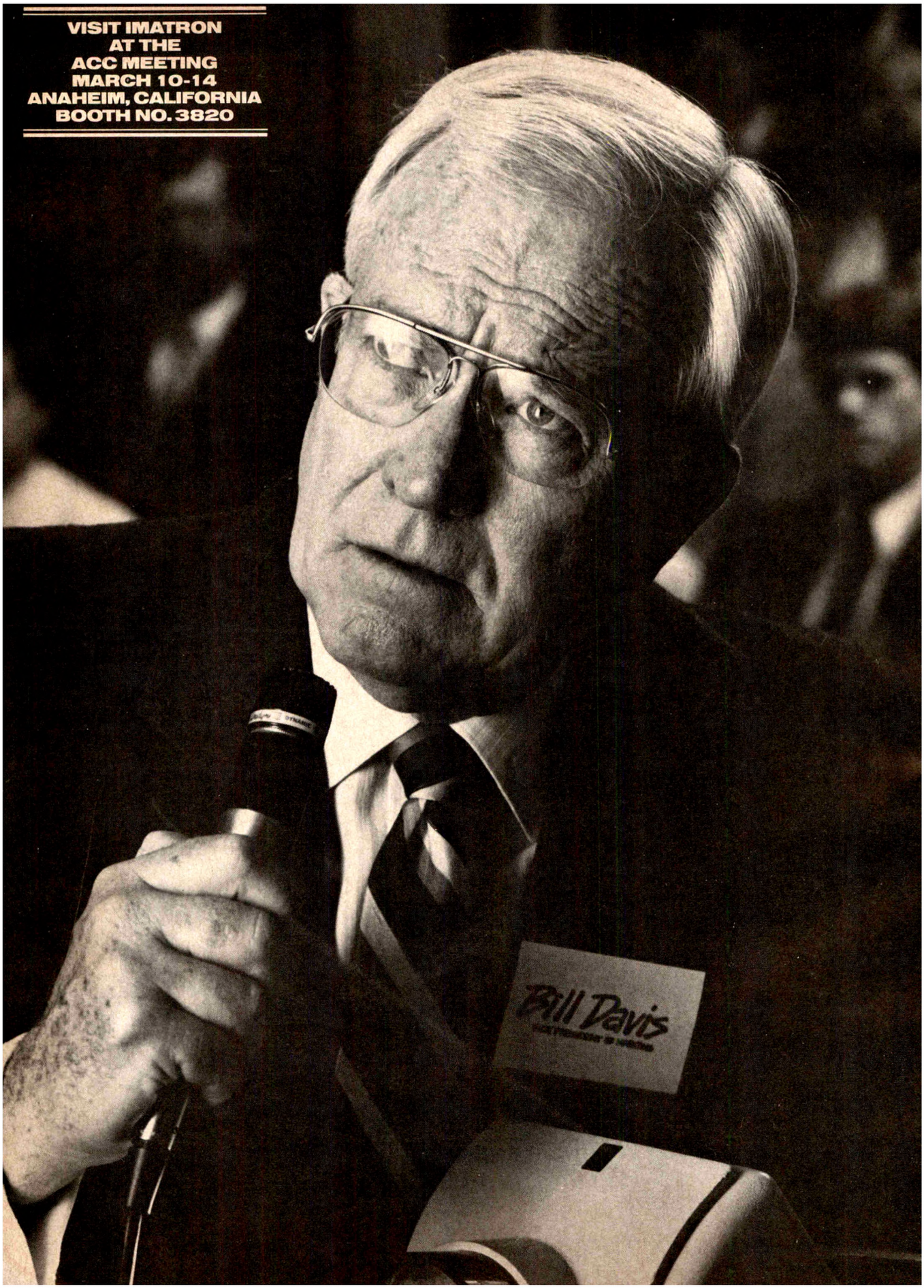
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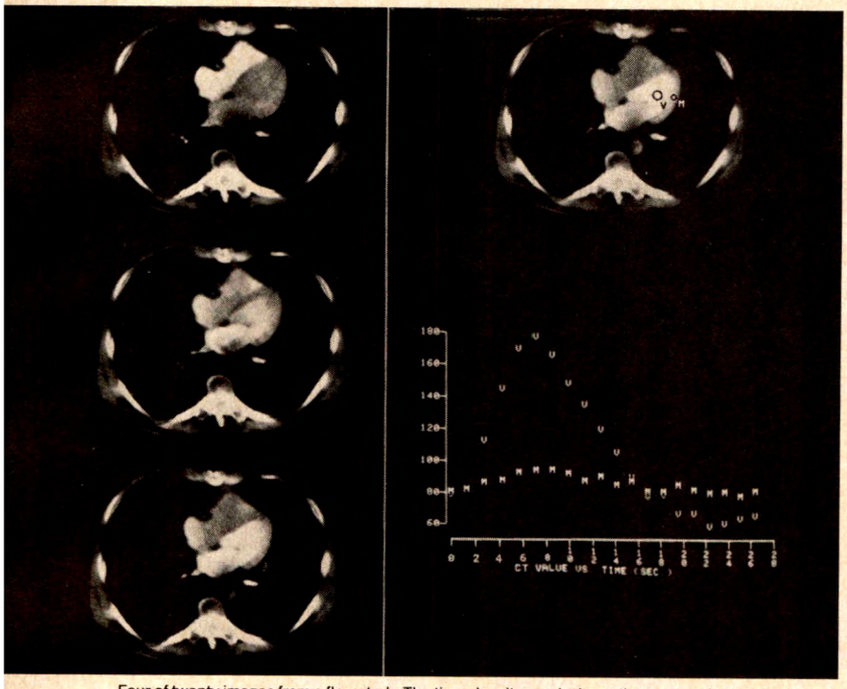

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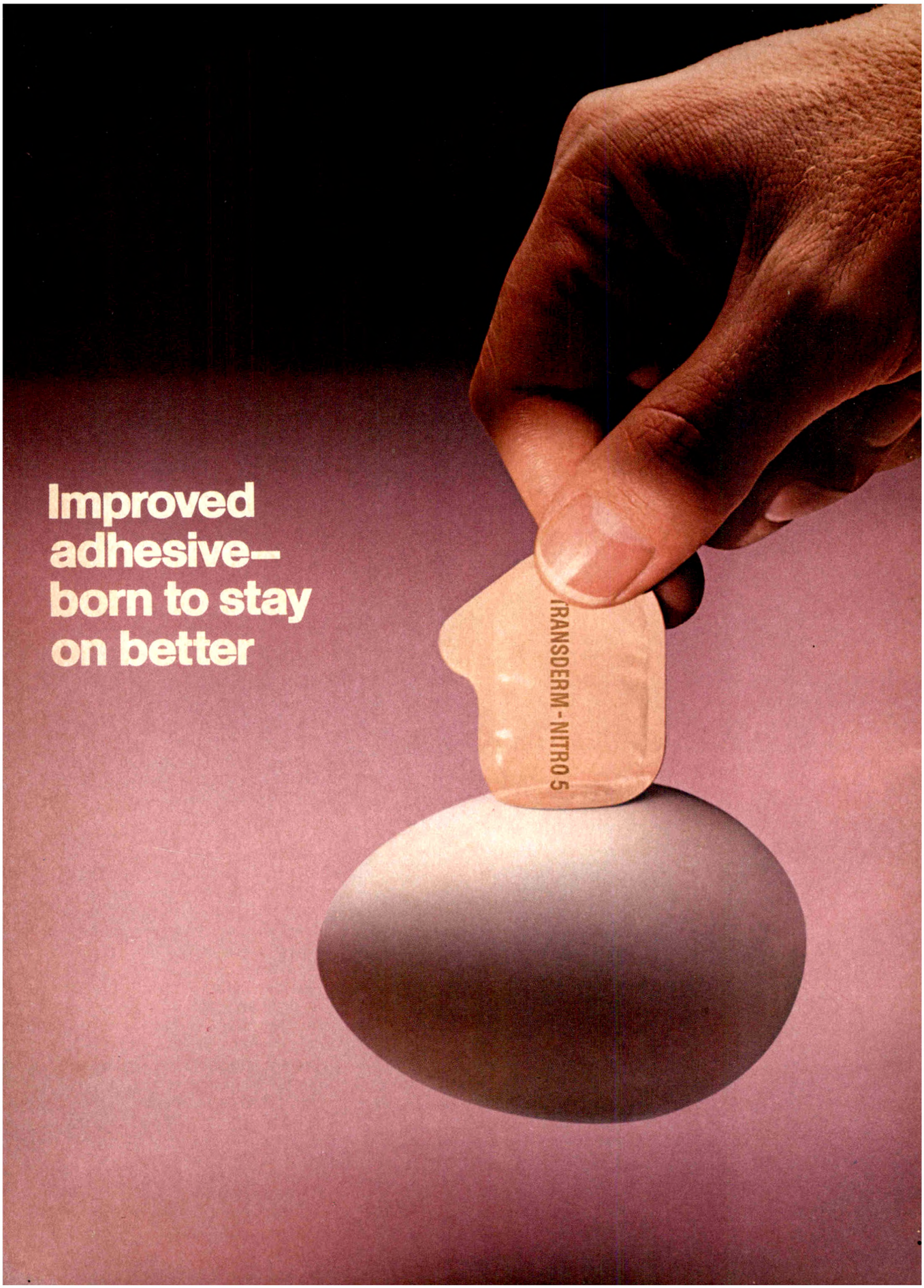
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ontraindicated in patients with intolerance to ganic nitrate drugs.

ransdermal nitroglycerin products are being marketed pending final luation of effectiveness by the FDA. (See Brief Summary of Prescribing rmation on the next page.)

a on file, CIBA Pharmaceutical Co.

Transderm-Nitro

(nitroglycerin)
Transdermal Therapeutic System

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)*

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

HOW SUPPLIED

Transderm-Nitro System Rated Release *in vivo*	Total Nitroglycerin in System	System Size	Carton Size
2.5 mg/24 hr	12.5 mg	5 cm^2	30 Systems (NDC 0083-2025-26)
5 mg/24 hr	25 mg	10 cm^2	30 Systems (NDC 0083-2105-26)
5 mg/24 hr	25 mg	10 cm^2	7 Systems (NDC 0083-2105-07)
10 mg/24 hr	50 mg	20 cm^2	30 Systems (NDC 0083-2110-26)
15 mg/24 hr	75 mg	30 cm^2	30 Systems (NDC 0083-2115-26)

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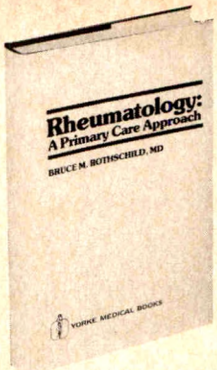
The Diagnosis and Treatment Oriented Approach to Rheumatology with the Primary Care Physician in Mind



Rheumatology
A Primary Care Approach

Written by:
Bruce M. Rothschild, MD
Director, Division of Rheumatology, University Health Sciences, The Chicago Medical School Chief, Section of Rheumatology, V.A. Medical Center North Chicago, Illinois

ISBN 0-914316-33-8, $42.50, 430 pp., illus., 1982.

What is Rheumatology: A Primary Care Approach?

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- a book meant to be used regularly, not read once and stored away on a library shelf
- the primary care physicians' answer to the huge, weighty tomes on Rheumatology which offer too little on diagnosis and treatment and too much on etiology and mechanisms of disease

Abbreviated Table of Contents

Section 1 **Investigative Techniques**
Section 2 **Patterns**
Section 3 **Management**

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"This book is a good primer for students, residents, and health professionals who would like a glimpse into rheumatology. It can be recommended for all but the specialist (but perhaps the specialist should read it, too, to see what those he is training are learning)."
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Initial therapy should start on the right course.

ypertensive patients

Minipress® for initial therapy
(prazosin HCl)

- Is effective when used alone
- Does not cause a significant incidence of sexual impotence, although it has been reported[1]
- Does not adversely affect blood lipids*[2]
- Does not lower heart rate, cardiac output or work capacity[3]
- Does not induce potassium wasting[1]
- Most common side effects with Minipress, generally mild and transient, are dizziness, headache, drowsiness, palpitations, and nausea. Syncope (sudden loss of consciousness) has been reported in about 0.15% of patients at the recommended initial dose of 1 mg.

*Minipress is not indicated for the treatment of hyperlipidemia.

Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

for Initial Therapy in Hypertension

Please see Minipress brief summary on following page

© 1983, Pfizer Inc.

Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

Brief Summary
MINIPRESS® (prazosin hydrochloride) Capsules ***For Oral Use***

INDICATIONS: MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: Minipress may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120–160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution. (See DOSAGE AND ADMINISTRATION.) Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsule of MINIPRESS. The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS in pregnancy has not been established. MINIPRESS is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See WARNINGS.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

OVERDOSAGE: Accidental ingestion of at least 50 mg of MINIPRESS in a two year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.

Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate MINIPRESS is not dialysable because it is protein bound.

TOXICOLOGY: Testicular changes, necrosis and atrophy have occurred at 25 mg/kg/day (60 times the usual maximum recommended dose of 20 mg per day in humans) in long term (one year or more) studies in rats and dogs. No testicular changes were seen in rats or dogs at the 10 mg/kg/day level (24 times the usual maximum recommended dose of 20 mg per day in humans). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS (prazosin hydrochloride) therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS (prazosin hydrochloride) alone for up to 51 months did not demonstrate changes in sperm morphology suggestive of drug effect.

HOW SUPPLIED: MINIPRESS is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

References: 1. Pitts NE: The clinical evaluation of prazosin, a new antihypertensive agent, in Prazosin Clinical Symposium Proceedings. Published as a special report by *Postgraduate Medicine*. New York, McGraw-Hill Book and Education Services Group, 1975, pp 117-127. **2.** Adapted from Kaplan NM: Summary: *J Cardiovasc Pharmacol* 4 (suppl 2): S265, 1982. **3.** Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in Prazosin Clinical Symposium Proceedings. Published as a special report by *Postgraduate Medicine*. New York, McGraw-Hill Book and Education Services Group, 1975, pp 45-52.

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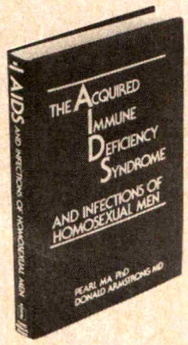
AIDS
An important new book on today's most virulent epidemic



From the Publishers of The American Journal of Medicine, The American Journal of Surgery, and Cutis

Acquire Immune Deficiency Syndrome (AIDS) and Infections of Homosexual Men

edited by **Pearl Ma, PhD,** and **Donald Armstrong, MD** with a foreword by **David J. Sencer, MD,** *Commissioner of Health, New York City; formerly Director, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services*
0-914316-38-9, 442 pages, illus., 1984, $39.50

The first scientific presentation to review all the facts in full

AIDS has become one of the most publicized diseases in modern times. It has produced fear and confusion in the general public and presented a formidable challenge to the medical community. Physicians and scientists have begun work on managing this epidemic, disease control centers continue to search for answers, and the federal government has declared AIDS the number one health priority of the nation. Understanding this disease demands cooperation between many different medical specialties, and papers on this subject have been published in many diverse journals not regularly read by individual specialists. Now, for the first time, two highly distinguished medical experts, Drs. Pearl Ma and Donald Armstrong, have coordinated in one easily accessible volume the complete range of interdisciplinary approaches to this complex disease, with contributions by the most eminent researchers and physicians in disease control and hospital teaching centers throughout the country. Comprehensive coverage is given to the entire spectrum of sexually transmitted diseases, and an additional section on diagnostic perspectives offers never before published material on why this syndrome occurs primarily among homosexual men. For any physician or other health care professional interested in the prevention and cure of this modern epidemic, this book is an indispensable guide to recognizing and treating AIDS and other sexually transmitted diseases.

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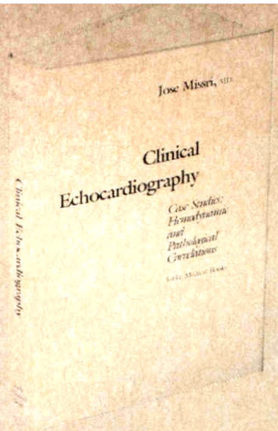

Clinical Echocardiography

Hemodynamic and Pathological Correlations

by José Missri, MD

0-914316-41-9, 282 pages, 173 illus., Oct. '84, $45.00

Dr. Missri has produced a unique contribution to the further understanding and application of Doppler echocardiography in the clinical practice of medicine. This book provides the reader with ready access to a body of knowledge so logically and clearly presented that its practical utility is undeniable. Enhanced by 139 halftones, 16 line drawings and 18 tables, the information contained within its concise 282 pages is easily absorbed. And the 315 references cited not only support the material presented but serve as an excellent guide to anyone interested in further in-depth reading.

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ISCHEMIC HEART DISEASE AND ACUTE MYOCARDIAL INFARCTION
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(nitroglycerin tablets, USP)

Before prescribing, please see full prescribing information.
A Brief Summary follows:

INDICATIONS
Nitroglycerin is indicated for the prophylaxis, treatment and management of patients with angina pectoris.

CONTRAINDICATIONS
Sublingual nitroglycerin therapy is contraindicated in patients with early myocardial infarction, severe anemia, increased intracranial pressure, and those with a known hypersensitivity to nitroglycerin.

PRECAUTIONS
Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. Nitrostat tablets are intended for sublingual or buccal administration and should not be swallowed. The drug should be discontinued if blurring of vision or drying of the mouth occurs. Excessive dosage of nitroglycerin may produce severe headaches.

ADVERSE REACTIONS
Transient headache may occur immediately after use. Vertigo, weakness, palpitation, and other manifestations of postural hypotension may develop occasionally particularly in erect, immobile patients. Syncope due to nitrate vasodilation has been reported. Alcohol may accentuate the cerebral ischemia symptoms.

METHOD OF ADMINISTRATION
One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every five minutes until relief is obtained. Nitrostat may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

HOW SUPPLIED
Nitrostat is supplied in four strengths in bottles containing 100 tablets each, with color-coded labels, and in color-coded Patient Convenience Packages of four bottles of 25 tablets each.

0.15 mg (1/400 grain):
N 0071-0568-24—Bottle of 100 tablets;
N 0071-0568-13—Convenience Package.

0.3 mg (1/200 grain):
N 0071-0569-24—Bottle of 100 tablets;
N 0071-0569-13—Convenience Package.

0.4 mg (1/150 grain):
N 0071-0570-24—Bottle of 100 tablets;
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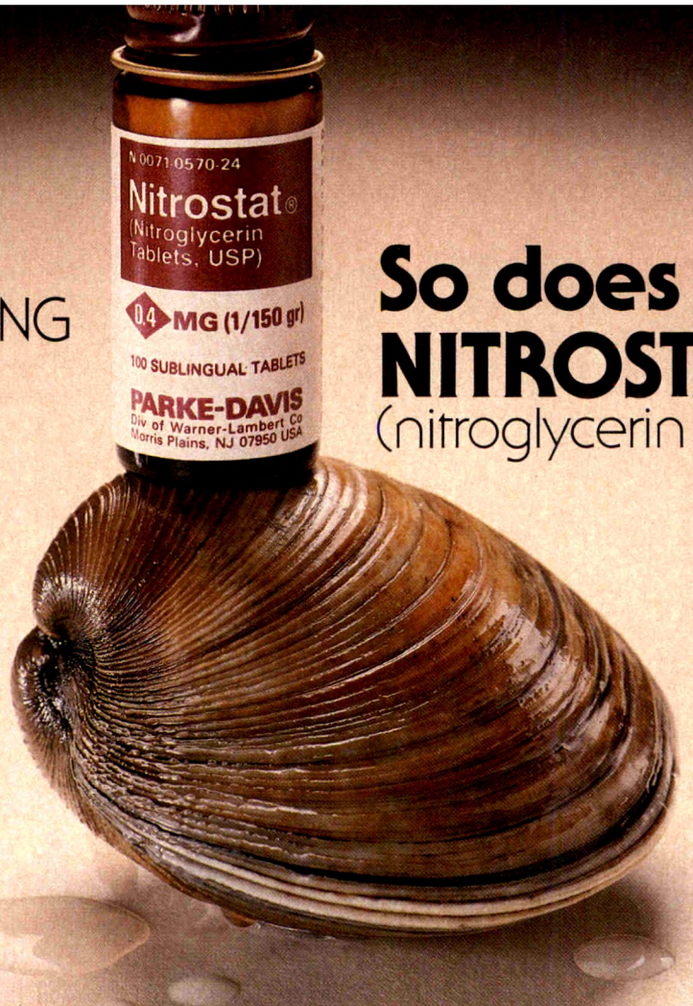

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Vascular Hemodynamic Impedance in Congestive Heart Failure

STANLEY M. FINKELSTEIN, PhD, JAY N. COHN, MD, V. ROSS COLLINS, MD, PETER F. CARLYLE, BS, and WENDA J. SHELLEY, BA

The objective of this study was to determine whether pulse-contour analysis could provide a measure of the differences in peripheral vascular state between patients with congestive heart failure (CHF) and healthy persons. Vascular hemodynamic impedance parameters were determined from brachial artery pressure waveforms recorded in 14 patients with CHF, aged 20 to 55 years (mean 36 ± 12) and in 7 healthy control subjects, aged 22 to 55 years (mean 33 ± 12). Cardiac output, heart sounds and electrocardiogram were also monitored. Cardiac output was 32% lower ($p < 0.01$) and heart rate was 43% higher ($p < 0.001$) in the CHF group than in the control group. The mean arterial pressure did not differ between groups. Systemic vascular resistance was 47% higher ($p < 0.05$) and distal vascular compliance 73% lower ($p < 0.001$) in the CHF group than in control group. Proximal vascular compliance was unchanged. These studies suggest that distal compliance assessed from pulse-contour analysis is a more sensitive and specific index than systemic vascular resistance to the vascular changes in CHF.

(Am J Cardiol 1985;55:423–427)

The characteristics of the peripheral vasculature are important in determining arterial pressure and left ventricular performance in patients with congestive heart failure (CHF). Peripheral vascular resistance is the parameter most frequently used to describe the peripheral vascular bed. However, recent studies suggest that frequency-dependent vascular impedance may be a more sensitive indicator of disease and therapeutic response.[1–11] The determination of this impedance requires Fourier analysis of simultaneously recorded pressure and blood flow waveforms, generally measured at the ascending aorta.

An alternative to this direct impedance measurement uses the peripheral arterial pressure pulse contour to derive vascular impedance properties.[12–15] This method requires only an arterial puncture to obtain a peripheral pressure signal, and thus offers the potential of practical clinical use. The resulting parameters are interpreted in terms of a Windkessel-type model of the vasculature and provide derived values for vascular compliance and resistance. In 1967, Goldwyn and Watt[12] proposed using such a model for interpreting the changes in arterial pressure waveshape in response to drug or disease intervention, and in 1976, Watt and Burrus[13] used a modified Windkessel for determining vascular resistance and compliance in hypertensive and healthy control subjects. These studies demonstrated that peripheral vascular resistance is increased and vascular compliance decreased in hypertensive patients.

More recently, Zobel et al[16] reported that the pulse-contour–derived distal compliance was a sensitive and drug-dependent indicator of a vasodilator response in dogs, and that this method was more sensitive than characteristic impedance or static resistance in monitoring vasodilator drug response.[17]

In the current study, the pulse-contour-Windkessel method has been applied to patients with CHF to determine if differences in vascular properties in these patients can be detected by such a method of analysis.

Methods

Studies were performed on 14 patients with CHF and 7 healthy control subjects. The CHF group consisted of 9 men

From the Division of Health Computer Sciences, Department of Laboratory Medicine and Pathology, and Division of Cardiology, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota. This work was supported in part by Grant HL 17871 from the National Institutes of Health, Bethesda, Maryland, and by a grant-in-aid from the American Heart Association, Minnesota affiliate, Minneapolis, Minnesota. Manuscript received July 23, 1984; revised manuscript received October 24, 1984.

Address for reprints: Stanley M. Finkelstein, PhD, Division of Health Computer Sciences, University of Minnesota, Box 511 Mayo Memorial Building, 420 Delaware Street SE, Minneapolis, Minnesota 55455.

and 5 women, 20 to 55 years (mean ± standard deviation 36 ± 12). The diagnosis of CHF was based on a history of fatigue, dyspnea, orthopnea, a third heart sound, pulmonary rales, jugular venous distention or pulmonary vascular congestion and radiologic or echocardiographic evidence of left ventricular dilatation. Pulmonary capillary wedge pressure ranged from 16 to 32 mm Hg, right atrial pressure from 2 to 22 mm Hg, and ejection fraction by radionuclide or contrast angiography from 10 to 33%. All subjects were in normal sinus rhythm at the time of the study. Heart failure was the result of coronary heart disease in 6 patients and idiopathic cardiomyopathy in 8 patients. All vasodilator drugs were withdrawn at least 72 hours before the study; digitalis and diuretic drugs were withheld for at least 12 hours before the study. All patients were clinically stable at the time of the study. The healthy control group consisted of 3 men and 4 women, aged 22 to 55 years (mean 33 ± 12). All study participants gave written, informed consent.

Pressure was recorded from the brachial artery using an 18-gauge, 2-inch Teflon® catheter connected to a Statham P23Db pressure transducer. This catheter-transducer system has an undamped natural frequency higher than 25 Hz and a damping coefficient less than 0.5, as measured by balloon pop in this laboratory. This frequency response is adequate for the pulse-contour technique.[15] Aortic valve closure was determined from heart sounds from the upper left sternal border. The beginning of the second heart sound indicated the onset of diastole, and the upstroke of the brachial artery pulse was used to mark the end of diastole. A thermodilution balloon flotation catheter was positioned in the pulmonary artery after percutaneous insertion into a brachial vein in the patients with CHF. Cardiac output was determined in triplicate by thermodilution. In normal subjects, cardiac output was measured by the thoracic impedance technique using the Minnesota Impedance Cardiograph model 30413.[18,19]

Waveforms were recorded for 30 seconds for each subject in a supine position, after at least 60 minutes supine rest after catheter positioning. All hemodynamic data were recorded on both paper and magnetic tape. Data were digitized using a 12-bit analog-to-digital converter, operating at 200 samples per second per channel. Digitized data were saved on disk for subsequent beat marking, signal processing and pulse-contour analysis. The onset and end of diastole for the brachial artery pressure waveform were marked on 6 consecutive beats and the modified Gauss-Newton parameter-estimating algorithm was run on each marked beat.[16] Each group of 6 consecutive beats was selected manually from each 30-second record, choosing the group with the most noise-free pressure and phonocardiogram signals as viewed by the operator. The diastolic waveform for each beat can be represented most generally as a third-order function:

$$P(t) = A_1 e^{-A_2 t} + A_3 e^{-A_4 t} \cos(A_5 t + A_6)$$

and the parameter-estimating algorithm calculated the optimal values for the Ai (i = 1 . . . 6), so that the estimated function fit the observed data with a minimum least squares error. These Ai coefficients, mean pressure and cardiac output were then used to determine the circuit elements (compliance, inertance and resistance) in a modified Windkessel model of the vasculature (Fig. 1), in which the measured brachial arterial pressure was taken as $P_2(t)$. Heart rate, pulse velocity and wave reflections do not figure directly in the determination of the circuit parameters. The results for each 6 consecutive beats were averaged, and the mean values were used in the statistical data analysis.

Regression analysis was used to determine relations between hemodynamic variables and impedance parameters within each group. Differences between the control and patient groups were determined using the unpaired *t* test. All data are presented as mean ± standard deviation.

Results

An example of the brachial artery pressure curves observed in the control and CHF groups is shown in Figure 2. The diastolic wave is the portion of the waveform studied in the pulse-contour procedure. The parameter-estimating algorithm was run on 6 consecutive beats for each subject and in all cases converged to a minimal error between estimated and observed brachial artery pressure of less than 2 mm Hg, over a pressure range of approximately 60 to 100 mm Hg. Coefficients of variation for distal compliance C2 over the 6 beats in each subject grouping ranged from 3 to 14%.

The data are summarized in Table I, which lists hemodynamic variables, pressure-contour parameters (A2, A4 and A5) and the vascular impedance parameters derived from the modified Windkessel circuit analysis. As expected, the major hemodynamic differences between the control and patient groups were a 49% lower

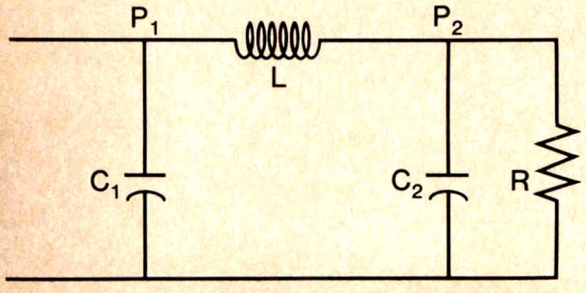

FIGURE 1. Modified Windkessel model of the arterial system used in the pulse-contour analysis. C_1 = proximal compliance (ml/mm Hg); C_2 = distal compliance (ml/mm Hg); L = inertance (mm Hg/ml/s^2); P_1 = proximal arterial pressure (mm Hg); P_2 = brachial artery pressure (mm Hg); R = peripheral resistance (dynes s cm^{-5}).

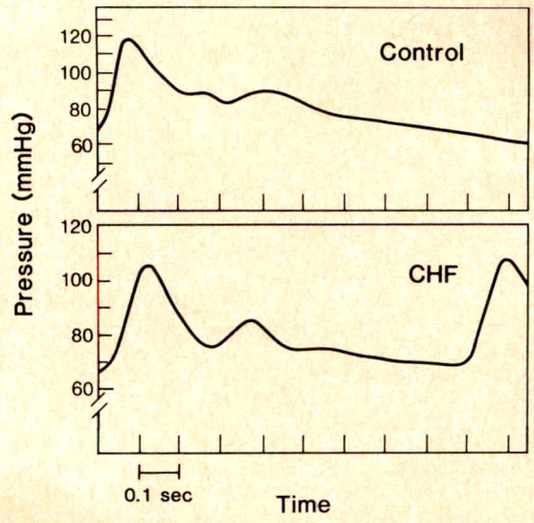

FIGURE 2. Brachial artery pressure pulse contour for the control and congestive heart failure (CHF) groups; an example from 1 subject in each group is shown.

TABLE I Hemodynamic Measurements, Pulse-Contour–Derived Parameters, and Windkessel Model Impedance Parameters for the Arterial Vasculature

Variables & Parameters	Healthy Controls (n = 7)	Congestive Heart Failure (n = 14)
Hemodynamic measurements		
MAP (mm Hg)	83 ± 10.8	75 ± 8.6
HR (beats/min)	67 ± 10.8	96 ± 17.6*
CO (liters/min)	6.10 ± 1.1	4.13 ± 1.32†
SV (ml/beat)	93.0 ± 21.2	47.3 ± 20.0*
Pressure contour parameters		
A2 (s^{-1})	0.67 ± 0.16	0.66 ± 0.26
A4 (s^{-1})	5.51 ± 5.48	15.66 ± 7.76†
A5 (s^{-1})	22.50 ± 8.65	22.21 ± 12.29
Impedance parameters		
R (dynes s cm^{-5})	1113 ± 183	1634 ± 587‡
C1 (ml/mm Hg)	1.83 ± 0.48	1.85 ± 1.26
C2 (ml/mm Hg)	0.15 ± 0.07	0.04 ± 0.03*
L (mm Hg/ml/s^2)	0.017 ± 0.005	0.062 ± 0.061

* $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$.
Data are expressed as mean ± standard deviation.
C1 = proximal compliance; C2 = distal compliance; CO = cardiac output; HR = heart rate; L = inertance; MAP = mean arterial pressure; R = peripheral resistance; SV = stroke volume.

stroke volume in heart failure ($p < 0.001$), a 43% faster heart rate ($p < 0.001$) and a 32% lower cardiac output ($p < 0.01$). Mean arterial pressure did not differ signficantly between the 2 groups. Systemic vascular resistance (SVR) in patients with CHF was increased by 47% ($p < 0.05$). Proximal compliance (C1), describing the elastic storage capability of the large arteries, is at least an order of magnitude larger than distal compliance (C2), which represents the elastic storage ability of the midsize arteries down to the arteriolar level. There was no significant difference in proximal compliance between the study groups. Distal compliance, however, was reduced by 73% in patients with CHF ($p < 0.001$). Inertance (L) was increased in heart failure, but because of the larger variability within each group these differences were not significant.

Six parameters are determined by the parameter-estimating algorithm that characterize the pulse-contour waveform. Three of these (A1, A3 and A6) are dependent on system initial conditions, and are not contributory in determining impedance properties of resistance, compliance and inertance. The 3 Ai parameters (A2, A4 and A5) listed in Table I are related to system structure and describe diastolic waveform oscillations and the exponential decay envelopes for these oscillations. Of these, only A4 was significantly different between the healthy control and CHF groups (189% higher in the CHF group, $p < 0.01$).

The age ranges were closely matched. Distal compliance and age were weakly correlated for the total population ($r = -0.44$) and for the CHF group ($r = -0.44$), as were SVR and age ($r = +0.41$ for the total population and +0.46 for the CHF group). Distal compliance was weakly correlated with cardiac output ($r = 0.56$) and heart rate ($r = -0.6$) and was not correlated with mean pressure. Multiple linear regression also failed to uncover any additional significant relations between vascular compliance and linear combinations of these hemodynamic variables. However, a strong correlation was seen between SVR and cardiac output ($r = -0.87$) in the CHF group. Resistance and distal compliance were uncorrelated in the CHF group.

Discussion

In previous animal and clinical studies we have modified and implemented the pulse-contour method of Goldwyn and Watt[12] and Watt and Burrus[13] and have shown that the Windkessel compliance parameters are more sensitive than either SVR or characteristic impedance as indicators of the vascular response to vasodilators.[16,17] Although the exact location of the vascular components cannot be determined from the model, because each element of the model is a composite functional representation, the model apparently can provide insight into the overall behavior of the vasculature.

Simon et al[14] reported a reduced compliance in hypertensive patients using a first-order Windkessel model that does not permit quantitative separation between large and small artery effects. Watt and Burrus,[13] using a third-order Windkessel model, found significant reduction in distal compliance in hypertensive subjects.[13] In the present study, proximal compliance was 1.83 and 1.85 ml/mm Hg and distal compliance was 0.15 and 0.04 ml/mm Hg ($p < 0.001$) for the control and CHF groups. These data agree with the Watt and Burrus results, and the sums of the proximal and distal compliances closely approximate the total compliance values reported by Simon. These data suggest that a reduction in distal vascular compliance is characteristic of heart failure, as well as of hypertension, and that this measurement may provide more insight into the site of vascular changes in these diseases than the simple calculation of SVR. A complete overlap in SVR between the normal subjects and patients with CHF was noted in the present study, whereas distal compliance values were quite discriminatory, as seen in the C2-R loci of Figure 3 and the scatterplots of Figure 4. One could speculate on the use of these vascular properties in discriminating between health and disease, particularly if such changes were to evolve early in the disease progression. For example, a C2 threshold value of 0.07 ml/mm Hg will clearly distinguish between the 2 groups. Control subjects have a relatively small range

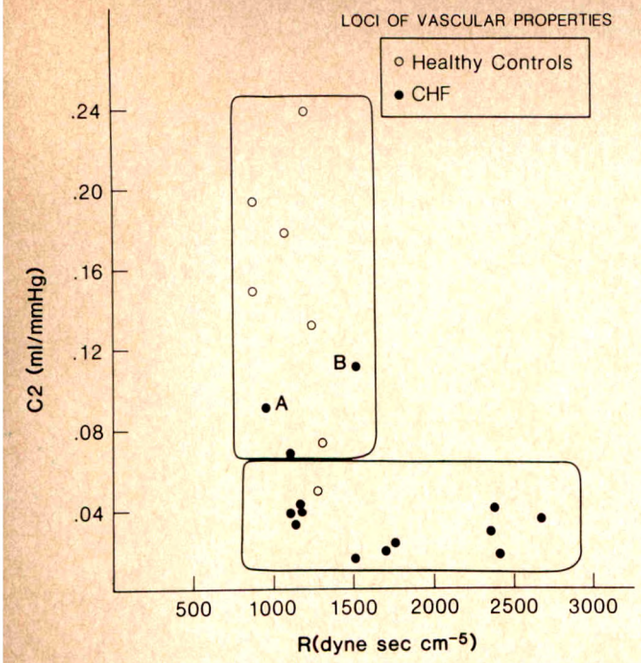

FIGURE 3. Loci of vascular distal compliance (C2) and peripheral resistance (R) for all subjects in the control group (n = 7) and the congestive heart failure (CHF) group (n = 14).

of resistance and a large range of distal compliance, whereas patients with CHF have the opposite pattern. Furthermore, the CHF subjects marked A and B in Figure 3 that fall within the control group locus had stroke volumes of 82 and 80 ml/beat, respectively, implying less severe heart failure. Thus the continuing movement of a subject's C2-R locus might provide a map of disease progression. Such a possibility must be tested in a prospective study to confirm its potential usefulness.

The correlation between the vascular parameters and cardiac output can be considered as a marker of the disease process rather than as an alternative indirect measure of cardiac output, since reports in the literature[13,14] and preliminary studies in this laboratory have also found significant changes in vascular compliance and resistance in hypertensive patients whose cardiac outputs are unchanged from that in control subjects but whose mean pressures are significantly elevated. That distal compliance and SVR are 2 independent properties of the vascular impedance load is further demonstrated in the compliance-resistance plot in Figure 3, showing the distinct loci for these vascular components in both the heart failure and control groups.

Pressure-contour parameter A4 changes significantly with heart failure and could be a potential marker for following vascular changes in heart failure (Table I). Because A4 describes the damping of the diastolic oscillation, the data suggest that patients with CHF have a more highly damped vascular system than normal subjects.

Vascular impedance by Fourier analysis has been reported extensively for the past 20 years in both animals and humans.[20–23] Pepine et al[4] reported that input resistance and characteristic impedance are significantly higher in CHF patients than in normal subjects, and suggested that the stiffer aorta might have significant influence on the pulsatile function of the failing left ventricle. These investigators also found that sodium nitroprusside lowered characteristic impedance.[5] In

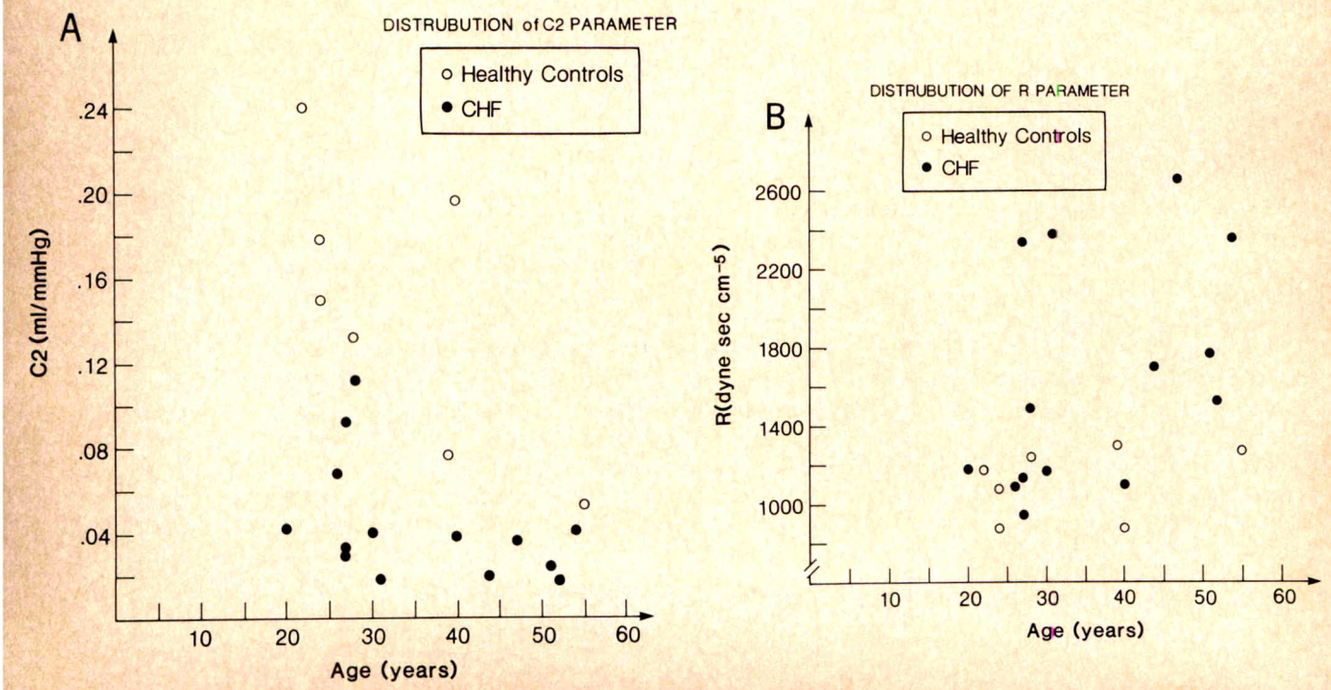

FIGURE 4. Scatterplots showing the distribution of vascular impedance properties with subject age for all subjects in the control and congestive heart failure (CHF) groups. **A**, distal compliance (C2) vs age; **B**, peripheral resistance (R) vs age.

contrast, Gundel et al[8] reported that characteristic impedance was essentially unchanged after nitroprusside. Yin et al[10] reported lower values for characteristic impedance at baseline than was reported by Pepine for a similar patient group, and like Gundel, did not find any change in response to nitroprusside. The value reported by Yin in heart failure (79 dynes s cm^{-5}) was actually lower than the value in normal subjects reported from the Pepine study (89 dynes s cm^{-5}).

Characteristic impedance is calculated by averaging impedance moduli for the higher-frequency components of the impedance spectrum. There is no standard for determining the frequency range used in this calculation, although frequencies from 2 to 12 Hz are frequently used. Because the impedance moduli at each of these frequencies may be highly variable, characteristic impedance represents a somewhat artificial figure of merit, which is highly dependent on the specific definition used for the calculation. Thus, differing methods may result in a wide range of values for characteristic impedance. The compliance parameters determined from the pulse-contour method might therefore be a more reliable indicator of vascular elastic behavior.

The current study using pulse-contour analysis and others using Fourier analysis show decreased vascular compliance in CHF. Many mechanisms have been suggested for the stiffer, less distensible, vascular behavior, including sodium retention and water logging, sympathetic nervous system stimulation, age, and a shift in compliance curve operating point. Because there was no significant difference in either age or mean pressure between groups in the current study, age and operating point shift could not be directly responsible for the observed compliance differences. Plasma norepinephrine and plasma renin activity are significantly elevated in heart failure, and the increased plasma norepinephrine is correlated with the hemodynamic and vascular resistance changes associated with heart failure.[24] Vascular compliance may also be affected by such sympathetic stimulation, and this possibility is currently under investigation. Further study is also needed to determine if this sympathetic response is the cause or effect of the decreased vascular compliance, increased vascular resistance, and hemodynamic changes observed in CHF.

Thus, although a functional relation between vascular compliance and the pathophysiology of heart failure is not available, these results implicate vascular compliance, particularly compliance of the more distal vessels, as the vascular property most significantly changed in heart failure. Further data are needed to assess the relation between these vascular changes and the severity of CHF and its response to therapy.

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Effects of Upright and Supine Position on Cardiac Rest and Exercise Response in Aortic Regurgitation

WEI FENG SHEN, MSc(Med), GARY S. ROUBIN, MB, PETER J. FLETCHER, MB, PhD, CHRISTOPHER Y-P. CHOONG, MB, BRIAN F. HUTTON, MSc, PHILLIP J. HARRIS, MB, DPhil, and DAVID T. KELLY, MB

The effects of upright and supine position on cardiac response to exercise were assessed by radionuclide ventriculography in 15 patients with moderate to severe aortic regurgitation (AR) and in 10 control subjects. In patients with AR, heart rate was higher during upright exercise, but systolic and diastolic blood pressure and left ventricular (LV) output were similar during both forms of exercise. LV stroke volume and end-diastolic volume were not altered during supine exercise. LV end-systolic volume increased and ejection fraction decreased during supine exercise, but both were unchanged during upright exercise. Of 15 patients, 5 in the upright and 12 in the supine position had an abnormal LV ejection fraction response to exercise ($p < 0.01$). Right ventricular ejection fraction increased and regurgitant index decreased with both forms of exercise and was not significantly different between the 2 positions. Thus, posture is important in determining LV response to exercise in patients with moderate to severe AR.

(Am J Cardiol 1985;55:428–431)

Radionuclide ventriculography during both supine and upright exercise has been used extensively for noninvasive assessment of cardiac function in patients with aortic regurgitation (AR).[1–4] Posture has important physiologic effects on the cardiovascular system at rest and during exercise.[5,6] Recent studies have revealed significant differences in the hemodynamic and cardiac functional response to exercise with different body positions in normal persons[7,8] and patients with coronary artery disease[8–10] or heart failure.[11] These effects of posture on exercise response may be especially relevant in patients with AR because of underlying alterations in loading conditions.[1–4] This study compares cardiac performance, at rest and during exercise, in both supine and upright positions, in patients with AR.

Methods

Patients: Fifteen patients (13 men, 2 women), aged 26 to 53 years (mean 42) with isolated, moderate to severe AR were studied (AR group). Eight patients had undergone cardiac catheterization, which documented isolated AR of angiographic grade 3/4, no mitral regurgitation and normal coronary arteries. The other 7 patients had clinical signs of isolated, moderately severe AR, with diastolic precordial basal murmur, pulse pressure greater than 55 mm Hg and cardiomegaly on radiograph. Echocardiography showed a left ventricular (LV) end-diastolic dimension greater than 6.0 cm, diastolic fluttering of the mitral valve and no coexistent valvular lesions. All patients who did not undergo catheterization were younger than 40 years and had no angina and segmental wall motion abnormalities on radionuclide angiography at rest and during exercise. All patients were in sinus rhythm.

Ten patients (9 men, 1 woman), aged 36 to 56 years (mean 45), with contrast angiographically normal LV function and coronary arteries were selected as a control group. All patients underwent catheterization because of atypical chest pain. The mean LV end-diastolic pressure did not differ before (6.8 ± 1.8 mm Hg) and after (8.0 ± 2.1 mm Hg) LV angiography. No patient had valvular disease and all had a normal electrocardiogram during exercise testing and were in sinus rhythm.

Study design: Studies were carried out at rest and during exercise in both supine and upright positions. The order of positions of exercise was randomly allocated; 6 patients exercised upright first and 9 patients supine first. A rest period of 20 minutes preceded each baseline measurement obtained and a 2-hour rest period separated the 2 exercise tests. Patients were positioned on an exercise table (Atomic Products) mounted with an electronically braked ergometer (Siemens Elema). Special care was taken to minimize the movement of

From the Hallstrom Institute of Cardiology, Department of Nuclear Medicine, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia. Manuscript received September 5, 1984; revised manuscript received November 5, 1984, accepted November 6, 1984.

Address for reprints: David T. Kelly, MB, Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, Camperdown N.S.W. 2050, Australia.

TABLE I Postural Effects on Hemodynamics and Cardiac Function

Variable	Supine		Upright	
	Rest	Exercise	Rest	Exercise
Control Group (n = 10)				
HR (beats/min)	69 ± 12	137 ± 22†	81 ± 8§	142 ± 19†‡
SBP (mm Hg)	119 ± 13	196 ± 17†	120 ± 13	199 ± 20†
DBP (mm Hg)	72 ± 7	92 ± 11†	76 ± 6	97 ± 11†
LVSV (ml)	76 ± 15	109 ± 26†	66 ± 15§	110 ± 30†
LVCO (liters/min)	5.1 ± 1.1	14.7 ± 3.4†	5.3 ± 1.0	15.2 ± 3.1†
LVEDV (ml)	121 ± 21	145 ± 31†	106 ± 23§	140 ± 39†
LVESV (ml)	46 ± 9	37 ± 11†	40 ± 10§	30 ± 12†§
LVEF (%)	62 ± 5	75 ± 6†	63 ± 6	79 ± 5†‡
RVEF (%)	52 ± 6	70 ± 7†	53 ± 6	69 ± 4†
RI	1.08 ± 0.12	1.11 ± 0.12	1.05 ± 0.12	1.13 ± 0.11
Aortic Regurgitation (n = 15)				
HR (beats/min)	70 ± 8	124 ± 16†	78 ± 11‡	130 ± 16†‡
SBP (mm Hg)	133 ± 13	196 ± 25†	138 ± 18	198 ± 25†
DBP (mm Hg)	62 ± 13	77 ± 20†	65 ± 12	73 ± 23†
LVSV (ml)	142 ± 42	134 ± 31	120 ± 38§	145 ± 40†‡
LVCO (liters/min)	10.1 ± 3.2	16.7 ± 5.1†	9.2 ± 2.5	18.6 ± 6.2†
LVEDV (ml)	243 ± 74	258 ± 67	221 ± 70‡	246 ± 66*
LVESV (ml)	100 ± 44	124 ± 60†	101 ± 47	104 ± 54§
LVEF (%)	60 ± 9	55 ± 14†	56 ± 11‡	59 ± 15‡
RVEF (%)	52 ± 5	63 ± 9†	51 ± 6	66 ± 9†
RI	2.36 ± 0.80	1.58 ± 0.28†	2.32 ± 0.84	1.56 ± 0.38†

*$p < 0.05$, †$p < 0.01$ rest vs exercise in the supine or upright position; ‡$p < 0.05$, §$p < 0.01$ supine vs upright at rest or during exercise.

DBP = diastolic blood pressure; HR = heart rate; LVCO = left ventricular output; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVSV = left ventricular stroke volume; RI = regurgitant index; RVEF = right ventricular ejection fraction.

the chest during exercise; the shoulders and the waist were fastened to the table with the restraining harness and seat belt. During supine exercise, the ergometer was positioned so that the axle was set at the table height. In the upright study, the patients sat at 80 to 90° to the horizontal with their feet 30 cm below the table height. In both positions, patients were instructed to hold but not grip the hand supports to avoid isometric contractions. Exercise in each position was continuous, multistage and symptom-limited. The initial workload of 15 W was increased by 15 W every 3 minutes. The pedal speed was held at a constant rate of 60 rpm. During exercise, the 12-lead electrocardiogram was recorded every minute and duplicate cuff measurements of blood pressure and radionuclide count data were obtained during the last 2 minutes of each exercise level. The phase IV Korotkov sound (muffling) was recorded as diastolic pressure.

Radionuclide determination of cardiac function: Red blood cells were labeled in vivo with 25 mCi of technetium-99m. Radionuclide data were collected with a single-crystal gamma camera (Technicare Ohio Sigma 420) as previously described.[12–14] LV end-diastolic volume and ejection fraction were estimated by a nongeometric technique validated in our laboratory.[12–14] LV end-systolic volume and stroke volume were calculated by end-diastolic volume and ejection fraction, and LV output was stroke volume times heart rate.

The right ventricular end-diastolic and end-systolic regions of interest were defined according to a standard method.[14] We previously showed that right ventricular ejection fraction measured by gated equilibrium method correlates well with that derived from the first-pass technique, and radionuclide regurgitant index (LV to right ventricular stroke count ratio) is closely related to angiographic regurgitant fraction.[14]

Statistical analysis: Results are given as mean ± standard deviation. Data at rest and during exercise at maximal workload in the 2 positions were analyzed by 2-way analysis of variance with Newman-Keuls multiple comparison test.[15] Difference between correlated proportions was compared by McNemar test.[16] A p value <0.05 was considered significant.

Results

Exercise tolerance and hemodynamics: The mean maximal workload achieved was similar during upright and supine exercise in the control (103 ± 26 vs 101 ± 23 W) and AR group (98 ± 40 vs 94 ± 38 W).

The hemodynamic and cardiac functional data are summarized in Table I. In each group, at rest and during exercise heart rate was higher in the upright position, and blood pressure and LV output were similar in both positions. Stroke volume was lower at upright rest in both groups, but was similar during both forms of exercise in the control group, and was higher during upright exercise in the AR group.

For both groups, heart rate, blood pressure and LV output increased from rest to exercise in the 2 positions. Stroke volume increased during both forms of exercise in the control group, but was unchanged during supine exercise in the AR group.

Cardiac function and regurgitant index: In each group, LV end-diastolic volume fell at upright rest, but was similar during both forms of exercise. LV end-systolic volume was smaller at upright rest in the control group, but was similar in both positions in the AR group. LV end-systolic volume was smaller during upright than during supine exercise in each group. At rest, LV ejection fraction was unaltered by the position in the control group, but decreased in the upright position in the AR group. LV ejection fraction was higher during upright than during supine exercise in both groups.

Exercise-induced changes in LV volumes and ejection fraction varied depending on both the position and the presence of AR. In control patients LV end-diastolic volume increased during both forms of exercise; in contrast, in patients with AR LV end-diastolic volume did not change during supine exercise. LV end-systolic volume decreased with exercise in the 2 positions for the control group, but it increased during supine exercise and was unchanged during upright exercise in the AR group. The mean LV ejection fraction increased during both forms of exercise in the control group, with all patients having an increase of at least 5% in the 2 positions. In contrast, LV ejection fraction decreased during supine exercise and was unchanged during upright exercise in the AR group. Of 15 patients, 12 in the supine position but only 5 in the upright position had an abnormal LV ejection fraction response to exercise (decreased or increased less than 5%) ($p < 0.01$) (Fig. 1).

In each group, there were no significant differences in right ventricular ejection fraction and regurgitant index between the 2 positions at rest and during exercise. During both forms of exercise, right ventricular ejection fraction increased in both groups; regurgitant index did not change in the control group and decreased in the AR group.

Discussion

This study of patients with moderate to severe AR shows that upright and supine body positions alter LV function at rest and during exercise. The supine position was frequently associated with an abnormal LV response to exercise in AR.

Effect of posture on hemodynamics and exercise tolerance: The higher upright heart rate at rest and during exercise in our control and AR patients may be a result of increased sympathetic and reduced vagal tone.[6] This agrees with previous findings in normal subjects[7,8] and in patients with heart disease.[9–11] In the upright position, LV stroke volume was lower at rest in both groups, presumably because of decreased LV preload (end-diastolic volume). During exercise, LV stroke volume was unchanged in the supine and slightly increased in the upright position for patients with AR, but neither differed significantly from the value at supine rest. These responses are different from those in the control group and may suggest a limited LV contractile reserve in these patients.[17] Because our patients had hemodynamically moderate to severe AR, these changes also may differ from those in patients with mild AR. Maximal attained external workload was comparable during both forms of exercise, probably because of a similar maximum forward cardiac output achieved,[18,19] since total LV output and regurgitant flow estimated by radionuclide regurgitant index[20] were similar during exercise in the 2 positions.

Effect of posture on left ventricular volumes and ejection fraction: The alterations in rest and exercise LV end-diastolic volume in the 2 positions may be explained by the effect of change in body position on systemic venous return,[21] as the degree of AR was not affected by position. During leg exercise, the blood volume pooled in the dependent regions is shifted into the intrathoracic space by the action of the muscle pump and sympathetic reflex venoconstriction.[6,19,22] Because systemic venous return is markedly enhanced by muscular exercise itself regardless of body position, LV end-diastolic volume would be expected to achieve similar levels during both supine and upright exercise. This agrees with previous findings in a preliminary study.[23]

A smaller LV end-systolic volume with similar systolic blood pressure at upright rest in control patients may represent an increased contractile state associated with the increased heart rate to compensate for the decreased end-diastolic volume.[7,8] In contrast, the LV end-systolic volume at rest was similar in both supine and upright positions in patients with AR. During both forms of exercise, the decrease in LV end-systolic volume seen in control patients probably resulted from the combination of effects of increased myocardial contractility and decreased afterload.[24] This was not observed in patients with AR, as LV end-systolic volume increased during supine exercise and was unchanged during upright exercise. The smaller LV end-systolic volume during upright exercise in both control and AR groups may result from a higher myocardial contractile state in the upright position[7,8] and an altered afterload.[24–26]

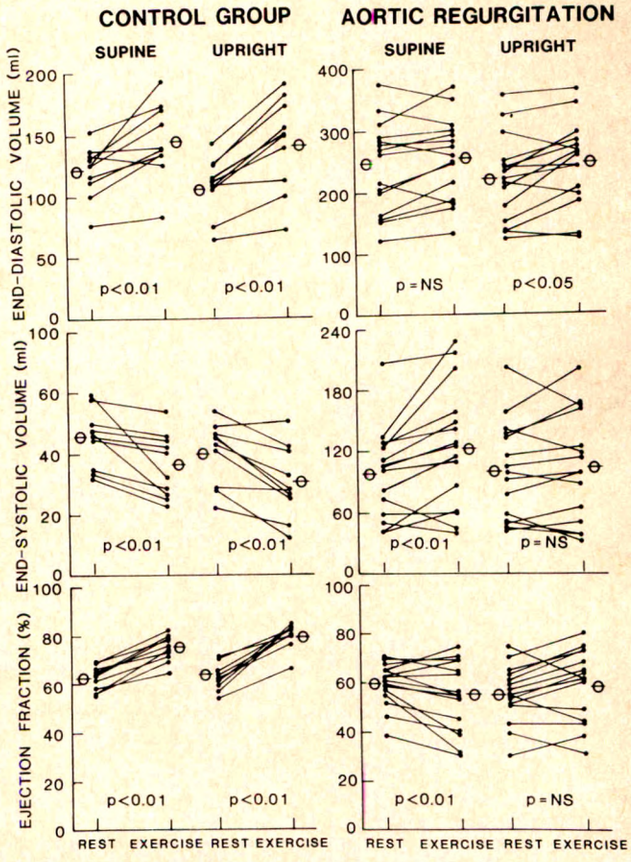

FIGURE 1. Effects of posture on left ventricular volume and ejection fraction response to exercise in the control group and patients with aortic regurgitation. Individual patients are represented by **closed circles** connected by **solid lines.** The **open circles** at the sides of each panel are the means. NS = not significant.

LV ejection fraction was similar at rest and increased significantly during both forms of exercise in control patients, consistent with previous findings in normal subjects.[7,8] In contrast, ejection fraction at rest was significantly lower in the upright position in patients with AR, and may be due to decreased preload without a compensatory increase in contractility. During exercise, mean LV ejection fraction decreased significantly in the supine position, with 12 of 15 patients failing to have an increase by at least 5%. This agrees with previous findings.[1,2] In contrast, mean LV ejection fraction was unchanged during upright exercise and was higher than that during supine exercise. An abnormal LV ejection fraction response to exercise was significantly less frequent in the upright position, suggesting that changes in loading conditions and contractility during exercise in the upright position may tend to mask LV dysfunction.[24–26]

Methodologic considerations: Separation of ventricular and atrial activities in the left anterior oblique projection may be more difficult in the supine than in the upright position. Since all our patients had no mitral regurgitation and atrial enlargement, the overlap between the ventricles and the atria may be small. A consistent approach was used for both positional studies in each patient, and LV and right ventricular regions of interest were defined on a stroke volume image. Thus, this source of error should be minor. In this study, as a fixed attenuation correction factor was applied for all patients; this may introduce some error in individual volume estimations.[27] However, our findings are based on changes in volume within individual patients, and the small error of volume estimation should not affect our conclusions.

In patients with moderate to severe AR, hemodynamics and cardiac function vary with posture at rest and particularly during exercise. Measurements in 1 position should not be compared with those obtained in another either at rest or during exercise in the individual patient. Because exercise-induced LV dysfunction occurs significantly more often during supine exercise, this position may be preferred for assessing LV functional capacity in asymptomatic patients with AR.

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Electrocardiographic Observations in Clinically Isolated, Pure, Chronic, Severe Aortic Regurgitation: Analysis of 30 Necropsy Patients Aged 19 to 65 Years

WILLIAM C. ROBERTS, MD, and PAUL J. DAY*

Certain electrocardiographic findings are described in 30 necropsy patients with clinically isolated pure, chronic, severe aortic regurgitation. They were 19 to 65 years old (mean 45). The hearts of the 22 men ranged in weight from 430 to 1,110 g (mean 717) and of the 8 women, from 375 to 950 g (mean 638). Four had grossly visible left ventricular (LV) scars. All but 1 patient was in sinus rhythm. The PR interval was >0.20 second in 8 patients (28%) and the QRS duration was ≥0.12 second in 6 patients (20%). Only 5 patients (17%) had 1 or more ventricular premature complexes recorded on the resting electrocardiogram analyzed. The mean QRS amplitude for each of the 12 leads averaged 23 mm. The highest mean QRS voltage occurred in leads V_2 and V_3 (each 38 mm), and the lowest in lead aVR (11 mm). The mean QRS voltage in V_5 was higher than in V_6 (33 vs 28 mm) and in 22 patients (73%) the QRS voltage in V_5 was higher than in V_6. The sum of the S wave in V_1 plus the larger of the R wave in V_5 or V_6 (Sokolow-Lyon index) averaged 51 mm and in only 22 patients (73%) was it >35 mm. The Romhilt-Estes voltage criteria for LV hypertrophy was fulfilled even less frequently, despite the severe degrees of LV hypertrophy in the patients studied. The total 12-lead QRS amplitude in the 30 patients ranged from 109 to 428 mm (mean 272) (10 mm = 1 mV) and in 27 patients (90%) it was >175 mm. The ratio of total 12-lead QRS voltage to heart weight in the 30 patients with aortic regurgitation was 0.42, only slightly higher than that in previously studied adults with severe aortic stenosis (0.39), an observation indicating that cavity dilatation does not magnify the QRS voltage generated by a given mass of myocardium.

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Although many studies are available on electrocardiographic findings in patients with aortic valve stenosis, few studies have described electrocardiographic findings in patients with chronic aortic regurgitation (AR). Electrocardiographic QRS voltage observations[1–7] in patients with chronic AR usually have been limited to analysis of the presence of left ventricular (LV) hypertrophy as determined by criteria proposed by Sokolow and Lyon[8] or Romhilt and Estes.[9] No studies of patients with fatal, pure, isolated AR have compared electrocardiographic findings during life to necropsy cardiac findings. Such a correlation is the purpose of this report. The amplitude of the QRS complexes in all 12 leads, in addition to that of certain R and S waves, was measured in all patients.

Definitions

The terms describing AR in the patients were defined as follows: *Clinically isolated*—valvular dysfunction limited to the aortic valve. Function of the mitral, tricuspid and pulmonic valves was normal. *Pure*—no peak systolic pressure gradient present between left ventricle and systemic artery. *Chronic*—evidence of severe AR for more than 6 months. *Severe*—AR graded 3+ or 4+/4+ by aortic root angiogram or symptoms of cardiac functional class III or IV (New York Heart Association criteria) and the symptoms attributable only to AR.

Patients

Inclusion criteria for this study were (1) presence of chronic, isolated, pure, severe AR; (2) age at death older than 15 years; (3) interval between aortic valve replacement and death within 2 months; (4) availability of 12-lead electrocardiogram (ECG) recorded either preoperatively or within 1 month of death; and (5) heart weight >350 g in women and >400 g in men. The ECG analyzed was always that obtained just before aortic valve replacement (19 patients) or in the patients who did not undergo aortic valve operation,[10] the one recorded in the last month of life. The amplitude of the QRS complexes was measured from the peak of the R wave to the maximal dip of the S or Q wave, whichever was greater (Fig. 1). The cardiac catheterization data were obtained just before aortic valve replacement (16 patients) or within 6 months of death in the patients who did not undergo aortic valve operation (6 patients).

Thirty patients fulfilled the inclusion criteria. Certain clinical and morphologic findings for these patients are summarized in Table I. In all 30 patients the clinical records were examined, the heart in each was examined initially and the hearts in 25 patients were reexamined. The amounts of coronary arterial narrowing present was determined by examination of 5-mm transverse sections of the 4 major coronary arteries by a method delineated elsewhere.[11] Of the 30 patients, the cause of the AR was infective endocarditis that had healed in 8,[10] cardiovascular syphilis in 6,[12] ankylosing spondylitis in 5,[13] Marfan's syndrome in 5,[14] uncertain cause

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received September 12, 1984, accepted October 2, 1984.

* Student, Saint Mary's College, Saint Mary's City, Maryland 20686.

Address for reprints: William C. Roberts, MD, Building 10A, Room 3E-30, National Institutes of Health, Bethesda, Maryland 20205.

in 4, trauma in 1[15] and systemic hypertension in 1.[16] The patients were 19 to 65 years old (mean 45); 22 (73%) were men and 8 (27%) were women. Of the 30 patients, 29 had evidence of congestive heart failure (New York Heart Association functional class III or IV); patient 2 (Table I) was asymptomatic but had aortic valve replacement because of a LV end-systolic dimension >55 mm by echocardiogram. Of the 30 patients, 22 had left-sided cardiac catheterization and aortic root angiograms. LV peak systolic pressures ranged from 88 to 190 mm Hg (mean 133), LV end-diastolic pressures from 8 to 80 mm Hg (mean 32) and systemic arterial end-diastolic pressures from 20 to 65 mm Hg (mean 42). Nineteen patients died of complications of aortic valve replacement; the other 11 died from chronic congestive heart failure secondary to the AR.

At necropsy, the hearts in the 22 men weighed 430 to 1,100 g (mean 717) (normal ≤400 g) and the hearts in the 8 women weighed 375 to 950 g (mean 638) (normal ≤350 g). These weights were total heart weights, not just LV weights. A grossly visible, transmural (involving all the inner half and a portion or all of the outer half of the wall) LV scar (healed myocardial infarct) was present in 4 patients, but none during life had a clinical event diagnosed as, or compatible with, acute myocardial infarction.

The comparison of means was done using an unpaired Student *t* test, the comparison of ratios was done using a chi-square test, and the correlation coefficients were calculated using a Pearson's product moment test. Significance was judged if the test yielded a p valve <0.05.

Results

General electrocardiographic observations: Electrocardiographic findings are summarized in Tables I and II. The total 12-lead QRS amplitude in the 30 patients ranged from 109 to 428 mm (mean 272) (10 mm = 1 mV), and in 27 patients (90%) it was >175 mm (Table II). The relation of the total 12-lead QRS voltage to heart weight in the 30 patients is illustrated in Figure 2. The method of measuring various QRS complexes for this measurement is illustrated in Figure 1. The mean QRS voltage for each of the 12 leads in each patient was 23 mm. The individual and mean QRS amplitudes in each of the 12 leads is displayed in Table II. The highest mean QRS voltage occurred in leads V_2 and V_3 (each 38 mm), and the lowest mean voltage in lead aVR, 11 mm. The QRS mean voltage in V_5 was higher than that in V_6 (33 mm vs 28 mm); in 22 patients (73%), the QRS voltage in V_5 was higher than that in V_6.

Various previously recommended electrocardiographic QRS voltage criteria (summarized by Murphy et al[17]) for LV hypertrophy and the frequency of their occurrence in our 30 patients with chronic AR are summarized in Table III. A few criteria have been slightly modified to allow the number designating the upper limit of normal to end in a 0 or a 5, and to allow the elevated value to always be greater than a certain number rather than equal to or greater than a certain number. Of the 18 criteria analyzed, only 1 upper-limit number was evaluated in 3, two values were analyzed in 14, and 4 values in 1. Thus, a total of 35 values were analyzed for the 18 criteria: 34 were measurements in millimeters of QRS voltage and 1 was a ratio. The 2 criteria that had the highest positive frequency were the sum of the tallest limb-lead R wave plus the deepest limb-lead S wave >15 mm (90%, 27 of 30 patients) and the sum of the voltage of the QRS complex in all 12 leads, >175 mm (90%). The sum of the S wave in lead V_1 plus the larger of the R wave in V_5 or V_6 was >35 mm in 22 patients (73%). The sum of the larger S wave of leads V_1 or V_2 plus the larger of the R wave of V_5 or V_6 was >35 mm in 26 patients (87%) and >40 mm in 22 patients (73%). The sum of the deepest S wave in leads V_1, V_2 and V_3 plus the tallest R waves in leads V_4, V_5 and V_6 was >35 mm in 26 patients (87%), >40 mm in 25 patients (83%), >45 mm in 22 patients (73%) and >50 mm in 21 patients (70%). The tallest R wave plus the deepest S wave in any single V lead was >35 mm in 19 patients (63%).

The S-wave amplitude in lead V_1 ranged from 9 to 60 mm (mean 23); the R-wave amplitude in lead V_5 ranged from 9 to 64 mm (mean 25) and in V_6, from 11 to 47 mm (mean 25). The sum of the S wave in V_1 and the larger of the R waves in either V_5 or V_6 (Sokolow-Lyon index) ranged from 22 to 110 mm (mean 51). The deepest S wave in leads V_1, V_2 and V_3 ranged from 12 to 70 mm (mean 38) and in 23 patients (77%) it was >25 mm. The largest precordial S wave was in lead V_1 in 3 patients (10%), in lead V_2 in 12 patients (40%), in lead V_3 in 13 patients (43%) and in V_4 in 2 patients (7%). The average S-wave amplitude was higher in lead V_2 than V_1 (40 vs 24 mm).

The largest R wave in leads V_4, V_5 and V_6 ranged from 12 to 64 mm (mean 30) and in 19 patients (63%) it was >25 mm; the largest precordial R wave was in lead V_4 in 2 patients (7%), in V_5 in 19 (63%) and in V_6 in 9 (30%). The mean height of the R wave in both leads V_5 and V_6 averaged 25 mm. The R wave in V_6 was larger than the R wave in V_5 in 9 patients (30%).

Of the 30 patients, 29 (97%) were in sinus rhythm. The PR interval in them ranged from 0.16 to 0.36 second (mean 0.21) and it was >0.20 second in 8 (28%) patients. The width of the QRS complex ranged from 0.06 to 0.14 second (mean 0.10); in 6 (20%) patients it was ≥0.12 second. The QRS axes are listed in Table II. Of the 30

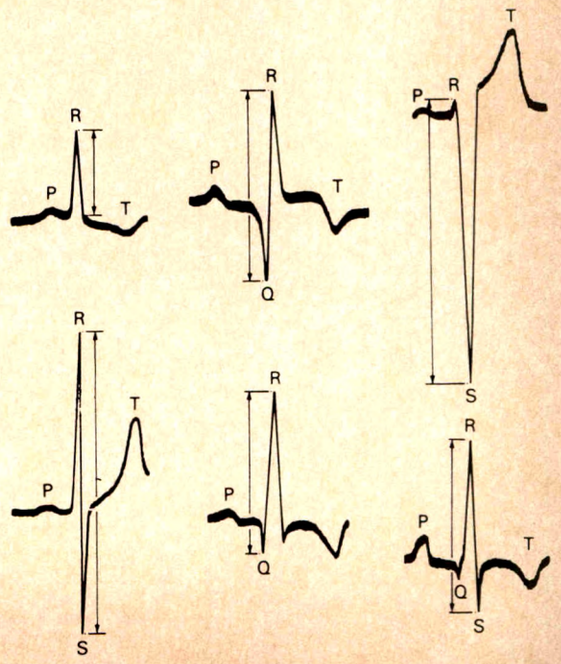

FIGURE 1. Method of measurement for various QRS complexes.

TABLE I Certain Clinical Morphologic and Electrocardiographic Features in 30 Necropsy Patients with Chronic, Severe, Pure Aortic Regurgitation

Pt	Autopsy No.	Age (yr) & Sex	Cause of AR	AP	Pressures (mm Hg) LV S	LV D	SA S	SA D	AR by Cine (1+–4+)	AVR	HW (g)	LV F	No. of 4 Major CA >75%	Electrocardiogram VR (bpm)	QRS axis (Degrees)	Intervals (sec) PR	QRS	VPC
1	A57-251	33M	IE	0	...	...	130	70	...	0	430	0	0	84	−40	0.27	0.14	0
2	A80-139	37M	IE	0	115	23	120	60	4+	+	610	0	0	90	−20	0.16	0.10	0
3	A69-254	39M	IE	0	140	20	140	38	4+	0	1010	0	0	68	0	0.20	0.12	0
4	71A-21	40M	IE	0	190	31	190	60	4+	+	575	+	0	72	+30	0.18	0.09	0
5	A70-117	45M	IE	0	120	50	120	50	4+	+	610	0	0	72	−15	0.20	0.11	0
6	71A-407	49M	IE	0	...	...	160	40	...	+	640	0	0	100	+30	0.18	0.11	+
7	A71-149	52F	IE	0	130	44	150	40	4+	+	500	0	0	75	0	0.15	0.10	0
8	A72-42	59M	IE	0	118	38	123	52	3+	+	840	0	0	70	+60	0.24	0.12	0
9	A58-280	19M	Syphilis	0	148	33	148	33	4+	0	750	0	0	100	+45	0.16	0.10	0
10	A61-192	37M	Syphilis	+	152	20	152	55	4+	0	600	0	0	66	+30	0.20	0.07	+
11	70A369	50M	Syphilis	+	...	...	160	60	...	0	720	+	2	90	−50	0.17	0.10	0
12	A65-106	55M	Syphilis	0	138	37	160	51	4+	+	940	0	3	75	−20	0.20	0.10	0
13	A64-223	56F	Syphilis	0	106	25	108	27	4+	+	800	+	3	72	+60	0.20	0.11	0
14	A77-241	65F	Syphilis	0	170	8	184	50	4+	+	710	0	1	81	+50	0.16	0.08	0
15	A61-274	34M	Anky Sp	0	100	22	120	25	4+	+	700	0	0	64	−30	0.26	0.10	0
16	A68-142	38M	Anky Sp	0	180	16	180	50	4+	+	1100	0	0	75	0	0.28	0.11	0
17	A61-99	52M	Anky Sp	0	160	18	168	30	4+	+	850	0	0	60	−15	0.36	0.14	0
18	A61-262	55M	Anky Sp	0	114	40	120	38	4+	0	680	0	0	82	−30	0.22	0.06	0
19	A66-127	57M	Anky Sp	0	...	...	200	80	...	0	500	0	0	110	0	0.17	0.09	0
20	A77-11	35F	Marfan	+	120	24	120	50	4+	+	375	0	0	66	−30	0.17	0.12	0
21	A58-206	36F	Marfan	0	...	...	130	40	...	0	700	0	0	95	−45	0.19	0.10	0
22	A65-64	41M	Marfan	0	100	30	100	40	3+	+	750	0	0	72	−10	0.20	0.10	+
23	A69-278	48F	Marfan	+	150	12	150	40	3+	+	520	0	0	72	+110	0.16	0.11	0
24	A59-169	59M	Marfan	0	190	25	200	80	3+	0	865	0	0	100	+20	...	0.08	+
25	71A27	34M	Uncertain	0	105	36	122	65	3+	+	460	0	0	84	−10	0.20	0.08	0
26	70A309	40F	Uncertain	0	...	...	180	60	...	0	950	0	0	70	+60	0.20	0.10	0
27	A64-102	41M	Uncertain	0	88	19	96	20	4+	+	920	0	0	75	+50	0.28	0.13	+
28	69A-135	59M	Uncertain	0	...	...	140	60	...	+	630	0	2	70	−20	0.167	0.08	0
29	A60-261	35M	Trauma	0	100	50	110	50	4+	0	550	+	0	85	+50	0.31	0.10	0
30	A68-325	51F	SH	+	...	...	210	80	...	+	600	0	0	76	−30	0.20	0.10	0
Mean or total		45 22M		5	132	28	139*	50*	22	19	696	4	5	79	+9	0.21	0.10	5

* Includes only the 23 patients in whom the systemic arterial pressure was measured directly at catheterization.

Anky Sp = ankylosing spondylitis; AP = angina pectrois; AR = aortic regurgitation; AVR = aortic valve replacement; CA = coronary artery; Cine-cineangiogram; D = end-diastole; F = grossly visible fibrosis; HW = heart weight; LV = left ventricle or left ventricular; S = peak systole; SA = systemic artery; SH = systemic hypertension; VPC = ventricular premature complex; VR = ventricular rate.

TABLE II Electrocardiographic QRS Amplitudes (in mm [10 mm = 1 mV]) in 30 Necropsy Patients with Chronic, Pure, Isolated Aortic Regurgitation

Pt	Electrocardiographic Lead												Total 12 Lead	S V_1	S V_2	R V_5	R V_6
	I	II	III	aVR	aVL	aVF	V_1	V_2	V_3	V_4	V_5	V_6					
1	7	7	12	5	9	9	11	33	42	42	29	34	240	10	33	22	32
2	13	20	23	14	19	19	11	14	11	12	15	11	182	10	12	12	11
3	12	8	15	9	12	10	30	56	52	37	24	50	315	27	54	23	47
4	15	15	12	15	11	10	31	33	20	48	35	28	273	29	28	35	28
5	8	30	28	18	15	26	32	72	44	58	50	29	410	25	62	48	28
6	9	12	8	7	9	7	33	37	40	41	32	28	263	27	32	31	28
7	7	8	7	7	7	7	26	48	47	28	30	20	242	24	48	27	20
8	8	9	5	7	6	7	24	25	12	17	17	16	153	23	24	16	14
9	5	18	17	11	6	17	25	53	49	55	36	19	311	17	36	21	17
10	9	7	4	8	5	4	18	29	35	14	31	29	193	20	31	32	30
11	16	5	14	8	16	11	16	31	38	34	30	15	234	16	30	23	15
12	20	7	24	10	21	15	27	58	46	17	23	31	299	28	49	29	31
13	13	18	21	10	15	19	21	28	32	29	39	36	281	20	24	27	34
14	11	14	9	11	8	9	10	12	15	20	30	20	169	9	16	18	17
15	19	17	28	13	23	19	31	64	74	24	68	48	428	30	59	64	44
16	29	13	21	22	27	9	50	58	72	42	21	50	414	50	59	9	42
17	21	11	12	14	17	4	21	18	16	8	27	27	196	15	15	26	24
18	9	4	11	6	10	8	14	18	31	31	27	24	193	13	16	15	21
19	19	21	8	21	11	12	50	54	37	70	45	26	374	39	38	37	25
20	11	8	6	8	8	5	14	34	46	40	42	24	246	7	13	15	12
21	21	18	35	12	28	26	39	44	37	39	45	37	381	31	39	37	30
22	21	14	19	18	16	10	64	74	62	20	46	27	391	60	72	50	27
23	9	32	42	13	30	37	8	23	28	38	62	62	384	9	21	12	16
24	9	9	13	5	12	12	15	29	34	16	26	22	202	17	35	16	14
25	5	5	6	5	5	4	9	22	18	6	15	9	109	8	18	14	8
26	12	9	10	9	12	5	32	39	40	27	20	35	250	29	37	10	31
27	8	11	6	8	8	9	31	52	76	52	25	29	367	22	52	11	27
28	11	15	8	11	6	11	14	19	26	33	29	19	202	13	19	20	15
29	10	8	11	6	10	9	22	22	30	24	30	25	207	21	21	29	24
30	18	20	15	18	13	17	35	25	16	15	29	28	249	33	22	28	26
Mean	13	14	15	11	13	13	25	38	38	32	33	28	272	23	34	25	25

Pt	Largest S V_1-V_3		Largest R V_4-V_6		Largest R 6 Limb Leads		Largest S 6 Limb Leads		R	S
	(mm)	(Lead)	(mm)	(Lead)	(mm)	(Lead)	(mm)	(Lead)		
1	33	V_3	32	V_6	8	aVL	11	III	5	11
2	12	V_2	12	V_5	16	aVL	17	III	12	17
3	54	V_2	47	V_6	12	I	10	III	12	10
4	29	V_1	35	V_5	15	I	15	aVR	15	7
5	62	V_2	48	V_5	18	II	17	III	9	17
6	39	V_4	31	V_5	12	II	3	aVL	7	0
7	48	V_2	27	V_5	8	I	8	aVR	8	5
8	24	V_2	16	V_5	9	I	9	aVR	9	2
9	40	V_4	21	V_5	11	II	7	AVF	3	6
10	35	V_3	32	V_5	10	I	8	AVR	10	4
11	35	V_3	23	V_5	15	I	13	III	15	13
12	49	V_2	31	V_6	23	aVL	22	III	18	22
13	29	V_3	34	V_6	19	aVF	11	aVR	11	0
14	16	V_2	18	V_5	14	II	12	aVR	10	0
15	68	V_3	64	V_5	20	aVL	22	III	18	22
16	68	V_3	42	V_6	30	I	23	aVR	30	20
17	15	V_1	26	V_5	19	I	16	aVR	19	12
18	27	V_3	21	V_6	9	I	11	III	9	11
19	38	V_2	46	V_4	20	I	19	aVR	20	7
20	16	V_3	15	V_5	11	I	8	aVR	11	5
21	39	V_2	37	V_5	29	aVL	32	III	19	32
22	72	V_2	50	V_5	23	I	18	aVR	23	15
23	27	V_3	16	V_6	37	aVF	29	aVL	2	41
24	40	V_3	16	V_5	11	aVL	11	III	10	11
25	18	V_2	14	V_5	3	I	3	aVR	3	3
26	39	V_3	31	V_6	9	I	10	aVR	9	4
27	72	V_3	27	V_6	7	I	7	aVR	7	2
28	19	V_2	25	V_4	11	I	9	aVR	11	8
29	32	V_3	29	V_5	10	I	10	III	10	10
30	34	V_1	28	V_5	20	II	17	aVR	17	0
Mean	38		30		15		14		12	10

single rest ECGs analyzed, 1 or more premature ventricular complexes were present in 5 patients (17%) (nos. 6, 10, 22, 24 and 27, Table I and II) and 1 or more premature atrial complexes in 1 patient (no. 2).

Comparison of men to women: No significant ($p > 0.05$) differences were observed between the 22 men and 8 women in mean age; percent with significant coronary arterial narrowing, LV scarring, angina pectoris or widened (≥0.12 second) QRS complexes; mean heart weight (717 vs 638 g); average total 12-lead QRS voltage (269 vs 275 mm); average Sokolow-Lyon index (52 vs 46 mm), or mean LV peak systolic pressure (134 vs 130 mm Hg).

TABLE III **Recommended or Modified Electrocardiographic Criteria for Determining Left Ventricular Hypertrophy as Applied to 30 Necropsy Patients with Severe Cardiomegaly from Chronic, Pure, Severe Aortic Regurgitation**

No.	QRS Complex Measured	Value Considered Upper Limit of Normal (mm)	No. (%) of 30 Patients Above Normal Limit
1a	$SV_1 + RV_5$ or V_6 (larger)	35	22 (73)
b	$SV_1 + RV_5$ or V_6 (larger)	40	18 (60)
2a	SV_1 or V_2 (larger) + RV_5 or V_6 (larger)	35	26 (87)
b	SV_1 or V_2 (larger) + RV_5 or V_6 (larger)	40	22 (73)
3a	SV_1 or V_2 (larger) + RV_6	35	25 (83)
b	SV_1 or V_2 (larger) + RV_6	40	21 (70)
4a	$SV_2 + RV_5$	35	24 (80)
b	$SV_2 + RV_5$	40	22 (73)
5a	Deepest $SV_1 - V_3$ + tallest $RV_4 - V_6$	35	26 (87)
b	Deepest $SV_1 - V_3$ + tallest $RV_4 - V_6$	40	25 (83)
c	Deepest $SV_1 - V_3$ + tallest $rV_4 - V_6$	45	22 (73)
d	Deepest $SV_1 - V_3$ + tallest $V_4 - V_6$	50	21 (70)
6a	Tallest R + deepest S in any V lead	35	19 (63)
b	Tallest R + deepest S in any V lead	40	16 (53)
7a	Deepest $SV_1 - V_3$	25	23 (77)
b	Deepest $SV_1 - V_3$	30	19 (63)
8a	Tallest $RV_4 - V_6$	25	19 (63)
b	Tallest $RV_4 - V_6$	30	14 (47)
9a	Deeper SV_1 or V_2	25	19 (63)
b	Deeper SV_1 or V_2	30	17 (57)
10a	Tallest RV_5 or V_6	25	26 (87)
b	Tallest RV_5 or V_6	30	14 (47)
11	$RV_6 > RV_5$	<1	9 (30)
12a	Tallest limb-lead R + deepest limb-lead S	15	27 (90)
b	Tallest limb-lead R + deepest limb-lead S	20	17 (57)
13a	$R_1 + S_3$	15	20 (67)
b	$R_1 + S_3$	20	14 (47)
14a	Tallest limb-lead R	10	21 (70)
b	Tallest limb-lead R	15	13 (43)
15a	Deepest limb-lead S	10	18 (60)
b	Deepest limb-lead S	15	11 (37)
16	R_1	10	15 (50)
17	S_3	10	13 (43)
18a	Total 12-lead QRS voltage	175	27 (90)
b	Total 12-lead QRS voltage	200	23 (77)

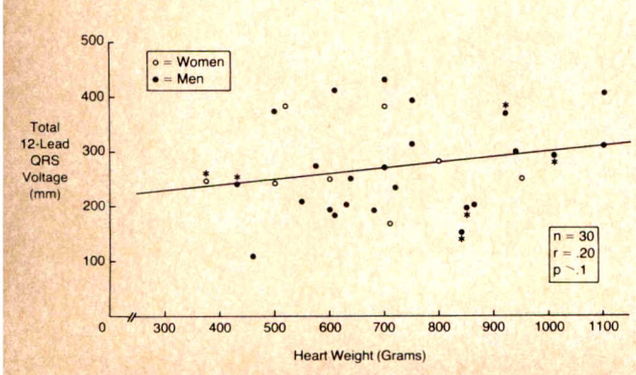

FIGURE 2. Relation of the total 12-lead QRS voltage (mm) to heart weight (grams) in the 30 patients with severe, pure aortic regurgitation. **Asterisks** designate the patients in whom the widths of the QRS complexes were at least 0.12 second.

Comparison of patients younger than 40 years and older than 40 years: No significant differences were observed between the 13 younger and the 17 older (older than 40 years) patients in sex ratio; percent with angina pectoris, widened QRS complexes or LV scarring; mean heart weight (677 vs 710 g); average Sokolow-Lyon index (50 vs 50 mm), or mean LV peak-systolic pressure (137 vs 129 mm Hg). The percent with significant (>75% cross-sectional area) coronary arterial narrowing was different (0 of 13 vs 5 of 17) ($p < 0.05$).

Comparison of patients with and without angina pectoris: No significant differences were observed between the 6 patients with and the 24 patients without angina in mean age; sex ratio; frequency of coronary arterial narrowing or LV scarring; average total 12-lead QRS voltage (287 vs 267 mm); mean Sokolow-Lyon index (55 vs 49 mm); or LV peak systolic pressure (117 vs 138 mm Hg). The frequency of widened QRS complexes was different (3 of 6 vs 3 of 24) ($p < 0.05$).

Comparison of patients with total 12-lead QRS voltage 250 mm or less to those with total voltage more than 250 mm: No significant differences were observed between the 17 patients with total 12-lead QRS voltage ≤250 mm and the 13 patients with larger total voltage in mean age, sex ratio, percent with significant coronary arterial narrowing, LV scarring, angina pectoris or widened QRS complexes; mean LV peak systolic pressure (135 vs 133 mm Hg), or mean heart weight (648 vs 760 g). The average Sokolow-Lyon index was different (39 vs 65 mm) ($p < 0.001$).

Comparison of patients with normal and abnormal Sokolow-Lyon indexes: No significant differences were observed between the 8 patients with normal and the 22 patients with abnormal (>35 mm) indexes in mean age; sex ratio; percent with narrowed coronary arteries, LV scar, angina pectoris or widened QRS complexes, or mean LV peak systolic pressure (131 vs 136 mm Hg). The average total 12-lead QRS voltage was different (210 vs 296 mm) ($p < 0.05$). The Sokolow-Lyon index in the 22 patients in whom this index was >35 mm ranged from 38 to 110 mm (mean 61) and their hearts weighed 430 to 1,100 g (mean 729); in the 8 patients in whom the Sokolow-Lyon index was <35 mm, the index ranged from 22 to 34 mm (mean 27) and their hearts weighed 375 to 865 g (mean 606).

Comparison of patients with normal and widened (more than 0.12 second) QRS complexes: No significant differences were observed between the 24 patients with QRS widths <0.12 second compared to the 6 with longer widths in mean age; sex ratio; percent with narrowed coronary arteries, LV scar or angina pectoris; mean heart weight (686 vs 738 g); average total 12-lead QRS voltage (276 vs 249 mm); mean Sokolow-Lyon index (51 vs 44 mm), or mean LV peak systolic pressure (138 vs 117 mm Hg). The frequency of angina pectoris was different ($p < 0.05$): angina was present in 3 of 24 patients with normal-width QRS complexes and in 3 of 6 patients with widened complexes ($p < 0.05$).

Comparison of patients with left ventricular peak systolic pressure less than 140 mm Hg to those with pressures greater than 140 mm Hg: No significant differences were observed between the 14 patients with the lower compared to the 8 patients with the

higher (>140 mm) pressures in age; sex ratio; percent with angina, coronary arterial narrowing, LV scar, or widened QRS complexes; mean heart weight (696 vs 746 g), average total 12-lead QRS voltage (271 vs 267 mm), or mean Sokolow-Lyon index (52 vs 44 mm).

Comparison of patients with hearts weighing 600 g or less to those with hearts weighing more than 600 g: No significant differences were observed between the 10 patients with hearts ≤600 g compared to the 20 patients with larger hearts in mean age; sex ratio; percent with angina pectoris, coronary arterial narrowing, LV scar or widened QRS complexes; average total 12-lead QRS voltage (252 vs 280 mm); mean Sokolow-Lyon index (45 vs 53 mm), or mean LV peak-systolic pressure (130 vs 135 mm Hg).

Comparison of patients with and without coronary arterial narrowing: The mean age was older among the 5 patients with narrowing >75% in cross-sectional area of 1 or more major coronary arteries compared to that among the 25 patients without (57 vs 42 years), and the percent with LV scarring was higher (2 of 5 vs 2 of 25) ($p < 0.05$). No significant differences were observed between the 2 groups in sex ratio; percent with angina or widened QRS complexes; mean heart weights (729 vs 688 g); average total 12-lead QRS voltage (243 vs 277 mm); mean Sokolow-Lyon index (47 vs 51 mm), or mean LV peak-systolic pressure (138 vs 140 mm Hg).

Comparison of patients with and without left ventricular scarring: Except for a higher frequency of coronary arterial narrowing in the patients with LV scars (2 of 4 vs 2 of 26) ($p < 0.05$), no significant differences between these groups occurred in age; sex ratio; percent with angina or widened QRS complexes; mean heart weight (661 vs 701 g); average total 12-lead QRS voltage (249 vs 274 mm); mean Sokolow-Lyon index (50 vs 50 mm) or mean LV peak-systolic pressure (132 vs 135 mm Hg).

Discussion

Patients with chronic severe AR generally have hearts of greater weight than that observed in other conditions.[18] Thus, these patients should have larger QRS voltages than observed in other conditions. In addition to measuring R and S waves in 1 or more leads for LV hypertrophy as suggested by many investigators and summarized by Murphy et al[17] and in Table III, we measured the total QRS voltage in all 12 leads in each patient and compared its usefulness to that of other voltage criteria for LV hypertrophy.

Because patients with chronic, severe AR generally have the largest human hearts, these persons would appear to be the ideal group to examine the usefulness of the various QRS voltage criteria for LV hypertrophy. Many studies, of course, have compared LV mass determined at necropsy[9,19] or by angiography[20] or echocardiography[21–23] to QRS voltage, but few of the previous studies have included patients with chronic, severe, pure AR. All previous studies have demonstrated that all QRS voltage criteria for LV hypertrophy are unreliable. The present study demonstrates the same finding, but in a group of patients with larger hearts than those studied previously. Our patients as a group had hearts that weighed roughly 2 times normal.

The Sokolow-Lyon index[8] (sum of the S wave in V_1 plus the larger of the R wave in either V_5 or V_6), the most widely used QRS voltage criterion for LV hypertrophy, was >35 mm, i.e., abnormal, in only 22 of our 30 patients (73%) whose mean heart weight was 696 g. The QRS voltage for LV hypertrophy advocated by Romhilt and Estes[9] fared even worse, although these 2 investigators also incorporated non-QRS-voltage criteria for LV hypertrophy. Only 8 of our 30 patients (27%) had an R wave in the 6 limb leads ≥20 mm and only 5 (17%) had an S wave in these leads ≥20 mm (In our Table III, we use the criteria >20 mm rather than ≥20 mm to aid in comparisons to other criteria.); 23 patients (77%) had an S wave in leads V_1, V_2 and V_3 ≥25 mm and 20 (67%) had an R wave in leads V_4, V_5 and V_6 ≥25 mm. (Again, in the table we modified these voltage criteria to >25 mm rather than ≥25 mm.) A total of 25 patients (83%), however, satisfied the Romhilt-Estes QRS voltage criteria in 1 or more of the 4 lead sites (R in limb leads ≥20; S in limb leads ≥20; S in V_1, V_2 and V_3 ≥25 and R in V_4, V_5 and V_6 ≥25 mm).

A better criterion of LV hypertrophy was the sum of the tallest R wave and deepest S wave in the 6 limb leads. This sum was >15 mm in 27 (90%) of 30 patients.

In contrast to the disappointing frequency of fulfillment of the Sokolow-Lyon, Romhilt-Estes and most other criteria (Table III) for LV hypertrophy in our 30 patients with chronic, severe AR, measurement of the sum of the height and depth of the QRS complexes in all 12 leads did appear useful. Although the upper limit of normal QRS voltage in each of the 12 electrocardiographic leads in adults without evidence of cardiac disease has been well established,[17,24–27] the upper limit of total 12-lead QRS voltage has not been established in human adults whose LV mass has been determined by necropsy or by an angiographic or echocardiographic means. It is likely, however, that the total 12-lead QRS voltage in adults over 30 or so years of age with normal sized hearts is <175 mm. Indeed, Richard B. Devereux (AJC Editorial Board Member), in his review of the present manuscript, stated that 12-lead QRS voltage was <175 mm in 87 of 92 clinically normal patients (95%) studied by him, P.N. Casale and P. Kligfield (unpublished observations), indicating that this criterion has good specificity (100 times number of normal subjects with negative test divided by total number of normal subjects tested). Using 175 mm as the upper limit of normal, 27 of our 30 patients (90%) had LV hypertrophy by this criterion.

In the present study we also examined 10 other variables, further analyzing each to compare patients with to those without 1 or more variables or to compare patients with greater than to those with less than a certain figure. A total of 90 comparisons were examined among the 10 variables. Of the 90, only 8 (9%) showed a significant ($p < 0.05$) difference in the variable analyzed. The 4 patients with transmural LV scars had a higher frequency of coronary narrowing (2 of 4 patients) than the 26 patients without LV scars (2 of 26 patients) ($p < 0.05$) and vice versa. Patients older than 40 years had a significantly higher frequency of coronary narrowing than did the younger patients ($p < 0.05$) and vice versa. Angina was significantly more frequent in pa-

TABLE IV Comparison of Total 12-Lead QRS Amplitude in Necropsy Patients with Chronic Aortic Regurgitation to Necropsy Patients with Aortic Valve Stenosis and Cardiac Amyloidosis

	Aortic Stenosis	p Value	Aortic Regurgitation	p Value	Cardiac Amyloidosis
No. of patients	50		30		30
Age (yr), range (mean)	16–65 (48)	NS	19–65 (45)	<0.001	21–93 (58)
Men (n)	36 (72%)	NS	22 (73%)	NS	15 (50%)
Women (n)	14 (28%)	NS	8 (27%)	NS	15 (50%)
Substernal pain (n)	34 (68%)	<0.01	11 (37%)	<0.05	4 (13%)
SA peak systole (mm Hg), range (average)	63–180 (112)	<0.001	96–200 (139)	<0.001	90–110 (104)
SA end-diastole (mm Hg), range (average)	34–88 (62)	<0.001	20–65 (42)	<0.001	60–80 (67)
Heart weight (g), range (mean)	380–880 (606)	<0.05	375–1110 (696)	<0.001	370–900 (532)
Narrowed coronary artery (n)	16 (32%)	NS	5 (17%)	NS	5 (17%)
Left ventricular scar (n)	7 (14%)	NS	4 (13%)	NS	4 (13%)
Total 12-lead QRS voltage (mm), range (average)	144–417 (257)	NS	109–428 (270)	<0.0001	58–199 (104)
Total 12-lead QRS voltage >175 mm, (n)	47 (94%)	NS	27 (90%)	<0.0001	2 (7%)

tients with QRS widths ≥0.12 second than in those with shorter QRS widths (3 of 6 vs 3 of 24) ($p < 0.05$) and, conversely, the patients with the normal Sokolow-Lyon indices had significantly lower average total 12-lead QRS voltage than did the 21 patients with an abnormal (>35 mm) Sokolow-Lyon index (210 vs 296 mm); conversely, the 17 patients with total 12-lead QRS voltages ≤250 mm had lower mean Sokolow-Lyon indexes than did the 13 patients with total 12-lead QRS voltages >250 mm (39 vs 65 mm) ($p < 0.001$).

Two other studies from this laboratory have used total 12-lead QRS voltage. One examined electrocardiograms in 50 necropsy patients with severe (LV systemic arterial peak systolic pressure gradients >50 mm Hg) aortic valve stenosis[28] and the other examined electrocardiograms in 30 necropsy patients with cardiac amyloidosis[29] (Table IV). Findings in these 2 groups of patients are summarized in Table IV and the findings are compared with those in the 30 patients with pure, chronic AR. The mean total QRS voltage was highest among patients with AR and lowest for those with amyloid. The percent of patients with AR or aortic stenosis having total 12-lead QRS voltage >175 mm was similar (90% and 94%), and 13 times higher than that in the amyloid group. The ratio of 12-lead QRS voltage to heart weight was slightly lower in the patients with aortic stenosis compared to those with pure AR (0.39 vs 0.42), indicating that cavity dilatation does not magnify the QRS voltage generated by a given mass of myocardium.

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Myxoid Degeneration of the Aortic Valve and Isolated Severe Aortic Regurgitation

WARREN M. ALLEN, MD, JACK M. MATLOFF, MD, and MICHAEL C. FISHBEIN, MD

Clinical and pathologic data were reviewed in 55 patients who had valve replacement for pure aortic regurgitation (AR) during a 6-year period. The clinical histories established the cause for AR in 34 cases: 11 rheumatic, 13 infective endocarditis, 4 congenital, 4 associated with aortic aneurysms and 2 the Marfan syndrome. In the valves from the other 21 patients, 13 had myxoid degeneration, defined as significant disruption of the valve fibrosa and its replacement by acid mucopolysaccharides and cystic change. Myxoid degeneration was also the primary pathologic abnormality in the 2 patients with the Marfan's syndrome, in 3 patients with a history of rheumatic disease and in 1 patient with a history of infective endocarditis. The patients with myxoid degeneration of uncertain origin were predominantly elderly (average age 63 years), had a long-standing history of systemic hypertension (77%) and had coronary artery disease (46%); 85% were male. In these patients the replacement valves were not larger than those of the other groups studied, indicating that dilatation of the aortic anulus was not a significant factor in the pathogenesis of the valve disease. These findings indicate that myxoid degeneration of the aortic valve is common (36% of all valves examined) and, in many cases, may be secondary to long-standing systemic hypertension.
(Am J Cardiol 1985;55:439–444)

The spectrum of disease found in the aortic valve and aorta is varied and complex. Pathologists studying valves removed at surgery are faced with the often difficult problem of determining a cause for valve failure, based on the end-stage pathologic findings at the time of operation. In addition to rheumatic and syphilitic disease, congenital malformation, infective endocarditis, trauma, and several metabolic, connective tissue and inflammatory diseases have been recognized as causing severe aortic regurgitation (AR).[1–5] However, little information is available concerning the relative frequency of these disorders in patients who undergo isolated aortic valve replacement for severe AR. In this study, we reviewed the clinicopathologic features of 55 patients who required aortic valve replacement for pure AR at our institution from 1976 to 1982.

Methods

Pathologic study: Gross and histologic findings were reviewed in 55 aortic valves removed during surgery for pure AR, both with and without coronary artery bypass grafting. Gross findings of interest were the number and thickness of valve cusps; presence of fusion of commissures; presence and degree (graded mild, moderate or severe) of calcification; and the presence of perforations, tears, fenestrations or vegetations.

Histologic sections of formalin-fixed material processed routinely or with decalcification were reviewed retrospectively. Sections were stained with hematoxylin-eosin and alcian blue/PAS. Based on a consensus of 2 investigators, histologic findings were graded 0 to +3, indicating no, mild, moderate or severe abnormalities. The abnormalities so graded included valvular calcification, deposition of mature collagen, presence of increased amounts of acid mucopolysaccharides (AMP), disruption of the valve fibrosa and cystic degeneration of the spongiosa layer. The histologic material was also assessed for the presence or absence of inflammatory or thrombotic vegetations. The diagnosis of myxoid degeneration was strictly limited to valves that had +2 or greater AMP deposition and a +2 or greater disruption of the valve fibrosa in the absence of calcification or more than +1 fibrosis. Because the base of the valve leaflet and the nodule of Arantius normally contain increased AMP and fibrous tissue, these areas were excluded from evaluation.

Clinical data: We searched the patients' charts for the following clinical information: age; sex; cardiac risk factors (including admission blood pressure, history and degree of hypertension, documented coronary artery disease, elevated serum lipids and smoking); history of rheumatic heart disease; and history of infective endocarditis, syphilis, congenital heart disease, Marfan's syndrome and other cardiovascular diseases. Catheterization data, operative findings and the replacement valve type and size were also reviewed.

From the Departments of Pathology and Thoracic Surgery, Cedars-Sinai Medical Center, Los Angeles, California. This study was supported in part by SCOR Grant in Ischemic Heart Disease HL 17651 from the National Institutes of Health, Bethesda, Maryland. Manuscript received March 26, 1984; revised manuscript received October 23, 1984, accepted October 26, 1984.

Address for reprints: Michael C. Fishbein, MD, Department of Pathology, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, California 90048.

TABLE I Cause of Aortic Regurgitation

Cause		n
Rheumatic heart disease		11
Endocarditis		13
Acute	5	
Old	8	
Congenital		4
Bicuspid valve	2	
Subaortic stenosis	1	
Tetralogy of Fallot	1	
Aortic aneurysm		4
Marfan's syndrome		2
Unknown		21
Myxoid degeneration	13	
		55

Using both the clinical and pathologic data, the patients were grouped according to the origin of their valvular insufficiency. The 6 groups were as follows: rheumatic heart disease, endocarditis (acute and old), congenital, associated with aortic aneurysm, Marfan's syndrome, and unknown (Table I). No patient had aortic stenosis or any functional abnormality of other cardiac valves.

Controls: To determine whether any observed pathologic changes were indeed associated with the valvular dysfunction, a control group of valves was also studied. This group consisted of 17 aortic valves: 12 from the county medical examiner's office and 5 from our necropsy service. These valves were from patients who died of noncardiac causes with no history of valvular disease.

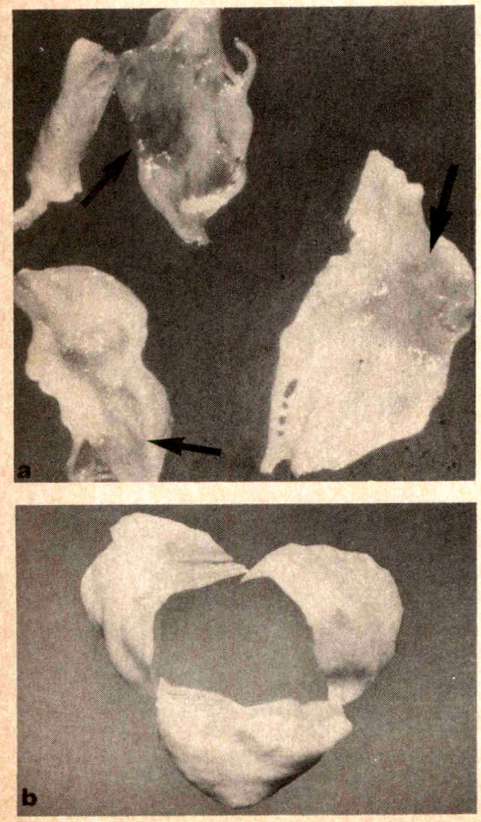

FIGURE 1. a, Myxoid degeneration of aortic valve. Thin, translucent regions are present in each leaflet (**arrows**). **b,** control aortic valve, which does not show this change.

Results

Clinical histories established the presence of rheumatic heart disease in 11 patients. In these predominantly male patients (Table II), aged 18 to 69 years, the period from onset of rheumatic disease was 15 to 50 years. Four patients had had additional episodes of infective endocarditis. In 4 patients the duration of heart failure was relatively long (3 to 7 years) and in the others it was recent (6 months or less) or not present. Two patients had coronary artery disease requiring simultaneous coronary bypass graft surgery. Two of 11 patients had a history of hypertension. Five of the excised valves showed fibrosis plus calcification, 3 showed nonspecific increased AMP and 3 of the valves had the histologic picture of myxoid degeneration. The replacement valves were, in general, large, with 9 of 11 measuring 27 mm or greater in diameter.

Thirteen patients had a history of endocarditis not associated with rheumatic heart disease. Five of these patients had acute endocarditis and presented with sudden-onset of AR. One patient had a ruptured cusp and 3 patients showed vegetations plus severe inflammation. The valve was severely calcified in one patient and had increased AMP in one; in the other 3 patients no underlying valvular pathology was found. Eight patients had a history of old bacterial endocarditis, ranging from 1 to 31 years in duration. None of these patients had a history of hypertension. Two of these patients had had congestive failure for as long as 3 years. The rest had a 6-month-or-less period of failure before valve replacement. The excised valves were fibrotic and often heavily calcified; fenestrations were prominent in 5. One valve showed only myxoid degeneration without fibrosis or calcification. The average replacement valve size was 26 mm.

Two patients with the Marfan's syndrome, a father and son, required valve replacement for AR. One had the simultaneous repair of an aortic aneurysm. Both of these valves showed pure myxoid degeneration and both required a 27-mm replacement valve.

Congenitally bicuspid valves accounted for AR in 2 patients. One valve was predominantly fibrotic with calcification and the other showed mild myxoid de-

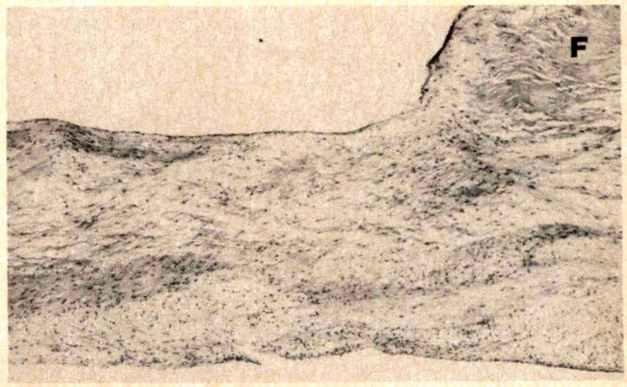

FIGURE 2. Key features of myxoid degeneration: disruption of the fibrosa (F) and increased acid mucopolysaccharides in the spongiosa. Alcian blue/PAS stain; original magnification × 16, reduced 51%.

TABLE II Clinical Characteristics of Patients with Rheumatic Heart Disease

Pt	Age (yr) & Sex	SAP (mm Hg)	SH	Interval (yr) Since Diagnosis	IE (no. of episodes)	CHF	AR (0–4+)	Replacement Valve	Increased AMP in Aortic Valve (0–3+)
1	69M	160/50	0	50+	0	9 mo	3+	27H	0
5	50M	116/60	0	40+	0	Recent	4+	25H	0
8	18M	130/40	0	11	2	4 yr	4+	27H	+
20	46M	128/65	0	24	0	7 yr	4+	29H	0
24	52M	180/78	+	37	2	5 mo	4+	27H	3+
25	69M	170/70	0	50+	0	5 yr	4+	27H	3+
34	28M	110/10	0	15	1	6 mo	4+	27B-S	+
35	62F	96/50	0	40+	0	3 yr	3+	21S-J	+
47	28M	150/40	0	18	0	6 mo	4+	27H	3+
48	63M	152/60	+	47	1	0	3+	29H	0
50	47F	160/70	0	30	0	0	4+	27S-J	0

AMP = acid mucopolysaccharides; AR = aortic regurgitation; B-S = Björk-Shiley valve; CHF = congestive heart failure; H = Hancock porcine valve; IE = infective endocarditis; SAP = systemic arterial pressure; SH = history of systemic hypertension; S-J = St. Jude Medical valve.

TABLE III Clinical Characteristics of Patients in Whom the Cause of Valvular Insufficiency Was Unknown (With Myxoid Degeneration)

Pt	Age (yr) & Sex	SAP (mm Hg)	SH	LVEDP (mm Hg)	CHF	AR (0–4+)	Replacement Valve	CAD
6	69F	236/70	+	24	Recent	4+	25H	+
9	57M	120/70	+	4*	0	4+	25H	+
10	62M	180/69	+	23*	1 yr	4+	25H	0
11	62M	154/80	+	30	0	2+	29H	+
12	66M	170/90	+	14	0	3+	25H	+
13	26M	180/60	+	12*	Recent	4+	27H	0
15	61M	110/70	0	13*	1 yr	3+	27H	0
18	73F	160/70	0		Recent	4+	23C-E	0
22	75M	164/76	+	27	Recent	3+	25C-E	0
26	74M	160/50	0	24	0	4+	25S-J	+
28	77M	180/84	+	14	Long, labile	4+	27H	+
37	50M	110/70	+	14*	+	3+	25S-J	+
44	66M	145/60	+	30*	1 yr	4+	25H	0

* Pulmonary capillary wedge pressure.
AR = aortic regurgitation (by cine); CAD = coronary artery disease; C-E = Carpentier-Edwards valve; CHF = congestive heart failure; H = Hancock porcine valve; LVEDP = left ventricular end-diastolic pressure; SAP = systemic arterial pressure; SH = history of systemic hypertension; S-J = St. Jude's valve.

generation. Two other valves were insufficient secondary to congenital anomalies and were removed after repair of other lesions: 1 from a patient with tetralogy of Fallot and 1 from a patient with subaortic stenosis. At operation both valves were redundant and thin, and prolapsed, with in the latter case, large fenestrations. Histologic sections of the valves showed focal fibrosis and mildly increased AMP.

An aortic aneurysm severe enough to require simultaneous patch grafting was found in 4 patients, in addition to one of the patients with Marfan's syndrome. All 4 patients had coronary artery disease and 1 patient had a long history of hypertension. The excised valves from 2 of these patients had enlarged cusps showing focal to severe calcification, and the valves from all 4 patients showed fibrosis and increased AMP. The replacement valves were large, averaging 28 mm.

The largest category of patients was the unknown group, in which no definite cause for AR could be found. This group was separated into 2 subgroups on the basis of valve pathology: 13 of the 21 valves showed the pathologic findings of pure myxoid degeneration (Fig. 1 and 2). Table III defines the clinical features of this subgroup. With one exception, the patients were age 50 years or older (mean 63 ± 13 [± standard deviation]), and 11 of the 13 were males. None had features or findings of Marfan's syndrome. Three patients, the 2 women and a 26-year-old man, had a history of cardiac murmur for 7 years or longer. Ten patients had long-standing systemic hypertension, described as severe in 4. Because one of our criteria for hypertension was current treatment with antihypertensive medication, many of the patients with a history of hypertension may have had normal systolic blood pressures on admission. Furthermore, because of the development of functional AR, a widened pulse pressure with a low diastolic pressure was often encountered. Patients with a history of unresponsive hypertension, those requiring multiple antihypertensive drugs or those with a history of hypertensive complications were classifed as severely hypertensive. The valves removed were usually thinned with extensive cystic change and myxoid degeneration. Increased AMP was found in both the spongiosa and fibrosa of the valves. As stated earlier, 2+ destruction of fibrosa was found in all of these valves. Many of the valves also had nodular thickening with large "pools" of myxoid material intermixed with fibrosis. Replacement valves averaged 26 mm in diameter.

TABLE IV Clinical Characteristics of Patients in Whom the Cause of Valvular Insufficiency Was Unknown (Without Myxoid Degeneration)

Pt	Age (yr) & Sex	SAP (mm Hg)	SH	LVEDP (mm Hg)	CHF	AR (0–4+)	Replacement Valve	CAD	Increased AMP in Aortic Valve (0–3+)
19	76M	130/65	0	29	40 yrs	4+	25H	0	0
21	74F	124/74	0	5	Recent	3+	23S-J	+	0
23	65M	170/70	0	6*	6 yrs	4+	27H	+	0
29	48F	110/60	+	36	Recent	3+	25C-E	0	+
30	45M	120/50	0	14*	Recent	4+	27H	0	+
31	68M	205/68	+	16	5 yrs	3+	23C-E	+	0
40	73M	130/100	+	27	10 yrs	4+	27C-E	0	+
41	72M	190/40	+	25	2 yrs	4+	27H	0	0

* Pulmonary capillary wedge pressure.
AR = aortic regurgitation (by cine); CAD= coronary artery disease; C-E = Carpentier-Edwards valve; CHF = congestive heart failure; H = Hancock porcine valve; LVEDP = left ventricular end-diastolic pressure; SAP = systemic arterial pressure; SH = history of systemic hypertension.

The other 8 patients in the unknown group are summarized in Table IV. Their clinical features are not distinctive, but include long-standing hypertension in 4 and severe coronary artery disease in 4. Two patients had presented recently with heart failure; the rest had received medication for 2 to 40 years. The excised valves showed a somewhat variable pattern with a combination of fibrosis, focal calcification and increased AMP. Replacement valves averaged 26 mm in diameter.

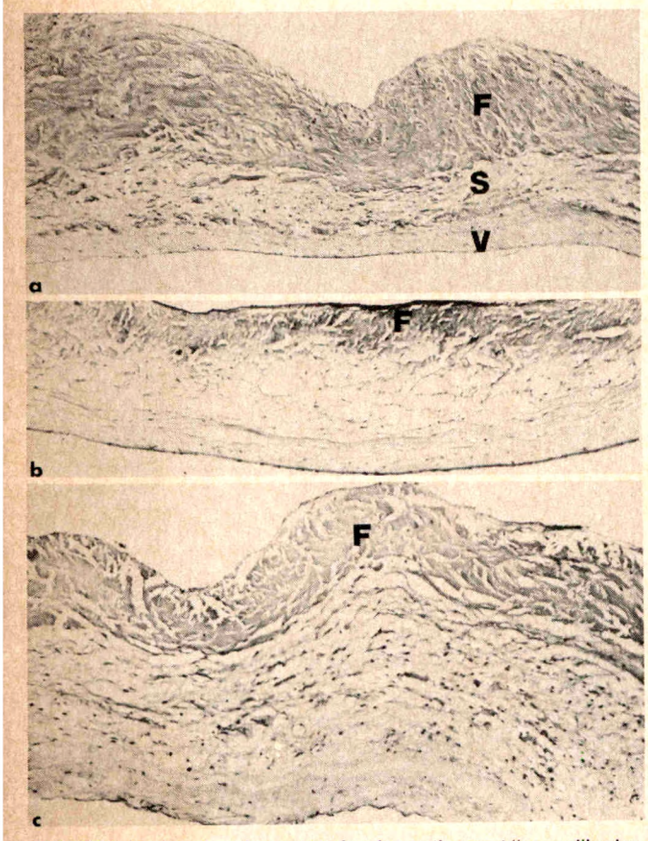

FIGURE 3. Aortic valves from control series. **a,** the most "normal" valve with distinct fibrosa (F), spongiosa (S) and ventricularis (V) layers. **b,** cystic change in the spongiosa. **c,** increased acid mucopolysaccharides in the spongiosa. In all of these examples (and all valves of the control series), the fibrosa is intact. Alcian blue/PAS stain; original magnification × 16, reduced 49.5%.

Follow-up of all patients at 2 months showed no complications. For 5 of the 13 patients follow-up at 1 year or longer was available. Of these patients, 2 were normal; 1 required a pacemaker for ventricular arrhythmias at 2 years; 1 patient had a mild perivalvular leak; and 1 died of a type I dissecting aortic aneurysm at 3 years. The last patient's prosthetic valve was described at operation as still functional.

Valves in the control group (n = 17 valves) were from patients 31 to 81 years old (mean 61); 10 were from men. Grossly, all valves were free of calcification, commissural fusion or vegetations (Fig 1). Focal areas of fibrous thickening were apparent as well as areas of relative translucency. Microscopic sections showed foci of 1+ cystic change limited to the spongiosa layer in 8 of the valves. Mildly (1+) increased AMP was present within the spongiosa in 7 valves. Most important, no valves had disruption of the fibrosa layer by AMP (Fig 3).

Discussion

Myxoid degeneration of the aortic valve was first described in a patient by Weaver et al, in 1957.[6] Read et al,[7] describing 3 such patients in 1965, considered it and the similar findings in the mitral valve as a possible forme fruste of Marfan's syndrome. Since then, several isolated cases of AR associated with myxoid degeneration of the valve leaflets have been reported.[8–14] In the past it was considered a rare finding, and there are few data regarding its frequency as a cause of AR. In contrast, myxoid degeneration of the mitral valve with prolapse is recognized as a common clinicopathologic entity. The reported frequency of mitral valve prolapse ranges from 6 to 17% of healthy adults.[8,15–17]

In this study of a large series of patients, myxoid degeneration was the primary pathologic abnormality in 36% (19 of 55) of all valves replaced for isolated, pure AR. In 2 patients the underlying disease was the Marfan's syndrome; in 3 there was a history of rheumatic heart disease, and 1 patient had a history of old bacterial endocarditis. In the remaining 13 patients a careful review of the clinical histories revealed no other commonly recognized primary cause for valvular insufficiency.

As demonstrated in our control group, it is well known that small amounts of increased AMP can be found in many valves. Using the strict criteria outlined in this

report and by others, pure myxoid degeneration requires a significant disruption of the valve fibrosa and its replacement by acid mucopolysaccharides, in the absence of fibrosis and calcification. Thus, it is actually the fibrosa that demonstrates degeneration. Whether the increased AMP is a primary or secondary phenomenon is uncertain. Presumably as a result of the degeneration of the fibrosa, the valve integrity is lost as the leaflets are progressively stretched and thinned, and the valve becomes incompetent. A defect in collagen biosynthesis has been suggested as an explanation for the floppy mitral valve syndrome by the finding of a marked increase in cross-linked procollagen and single chain procollagen.[18] Similarly, electron microscopy studies of floppy valves have shown granular cells containing collagen.[19,20] These cells are similar to those found in valves from patients with Hurler's syndrome, and may be related to an abnormal interaction between newly secreted collagen and acid mucopolysaccharides.

As with the mitral valve, the pathogenesis of myxoid degeneration of the aortic valve is uncertain. We studied the clinical features most likely to be associated with valve degeneration (Table V). Patients in the myxoid degeneration group have a fairly uniform clinical profile—85% were male, all except 2 were in their seventh decade or older, and they had a high incidence (46%) of coronary artery disease—but none of these features distinguishes it significantly from other groups. Although clinically the patients were free of features of Marfan's syndrome, we compared the replacement valve diameter among the different groups to see if valve stretching may have been related to a dilated aortic anulus, as in Marfan's syndrome. Valve diameters in the myxoid degeneration group were not larger than those of the other groups with AR. Although an enlarged anulus surely may contribute to valve stretching and thinning, it does not appear to explain AR in the cases of myxoid degeneration we observed.

Hypertension does appear to be associated with valve degeneration, and may be causally related. Long-standing hypertension was found in 10 of 13 patients (77%) in the myxoid degeneration group compared with 18% in all of the other groups combined. Although our groups are small, this difference was statistically significant (by chi-square analysis, $p = 0.003$).

The association of hypertension and AR that we have documented pathologically has been suspected clinically since 1920, when Osler noted the presence of diastolic murmurs in arterial hypertension.[21] Phonocardiographic evidence was obtained in 1960 by Puchner et al,[22] who documented diastolic murmurs in 15 patients with hypertension. They believed that this indirect evidence of AR was related to hypertension, but the clinical features of their patients were not fully described and there was no pathologic follow-up on the valves. Waller et al[23] recently described 4 patients with hypertension in whom severe AR developed, requiring valve replacement. A detailed histologic analysis of the valves was not included in their study, but there was no mention of valve thickening or calcification. The means by which hypertension effects such a change can only be surmised, but may be related to accelerated disruption of collagen in elderly patients who may have limited capacity for collagen synthesis, thus causing attrition and progressive degeneration of the valve fibrosa.

TABLE V Clinical Features of Patients with Aortic Regurgitation

Cause	Mean Age (yr)	CAD	Mean Prosthetic Valve Diameter (mm)	SH
Unknown				
Myxoid degeneration	63	6/13	26	10/13*
Other	65	3/8	25	4/8
Rheumatic	49	2/11	27	2/11
Endocarditis				
Acute	43	0/5		0/5
Old	51	3/8	26	0/8
Aortic aneurysm	67	4/4	28	1/4
Marfan's syndrome	37	0/2	27	0/2

* $p = 0.003$
CAD = coronary artery disease; SH = systemic hypertension.

The severity of the degeneration in our 13 patients indicates a pathologic process that may carry over into the postoperative period. A perivalvular leak developed in 1 patient and fatal dissecting aortic aneurysm in another. This is in keeping with reports of increased postoperative problems in myxoid degeneration of the mitral valve,[8] although the pathogenetic mechanisms may be different.

One other feature of note is that 3 of our patients with myxoid degeneration, the 2 female patients and a young male patient all had long-standing asymptomatic cardiac murmurs. Perhaps these patients, who do not fit well into the elderly male hypertensive category, represent a group with an inherent congenital defect but without other traits of Marfan's syndrome. These patients may or may not remain asymptomatic until the elderly period. Their high systolic pressures may be simply a reflection of their AR rather than a generalized hypertensive process. However, their inclusion in the total group emphasizes our overall finding that myxoid degeneration of the aortic valve is not rare, and may in fact be one of the most common pathologic entities associated with severe AR.

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Visken® (pindolol)

5-mg and 10-mg Tablets

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE
Visken® (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/ kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

	Total (Volunteered and Elicited)		
Body System/ Adverse Reaction	Visken (pindolol) (N = 322) %	Active controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

* Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

More than 7 million patient-years of experience

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and non-thrombocytopenic purpura.

Gastrointenstinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥ 80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 5 mg b.i.d. alone or in combination with other antihypertensive agents. An antihypertensive response usually occurs within the first week of treatment. Maximal response, however, may take as long as or occasionally longer than two weeks. If a satisfactory reduction in blood pressure does not occur within 3-4 weeks, the dose may be adjusted in increments of 10 mg per day at these intervals up to a maximum of 60 mg per day.

HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05).

[VIS-Z3 6/15/83]

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Visken®
(pindolol)

A different kind of beta blocker

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

"Why do you prefer Visken® (pindolol) for your older hypertensive patients?"

"Among other patient types, older hypertensive patients appear to respond well to Visken therapy."

When you're asked about Visken therapy, you'll want to have the answers.

brief summary of prescribing information on next page.

Pharmaceutical Division
SANDOZ, INC.
East Hanover, NJ 07936

VISKEN FULFILLMENT
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CHICAGO, IL 60606

Please send me clinical background information on Visken (pindolol). I'm interested in how it acts as a beta blocker and a partial beta agonist at the same time to control blood pressure and maintain cardiac output. How does this dual action benefit my patients over 55 who may have elevated blood pressure, impaired cardiac function and increased total peripheral resistance?

VIS-185-9

Visken®
(pindolol) 5-mg and 10-mg Tablets

Send me the answers.

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(please print)

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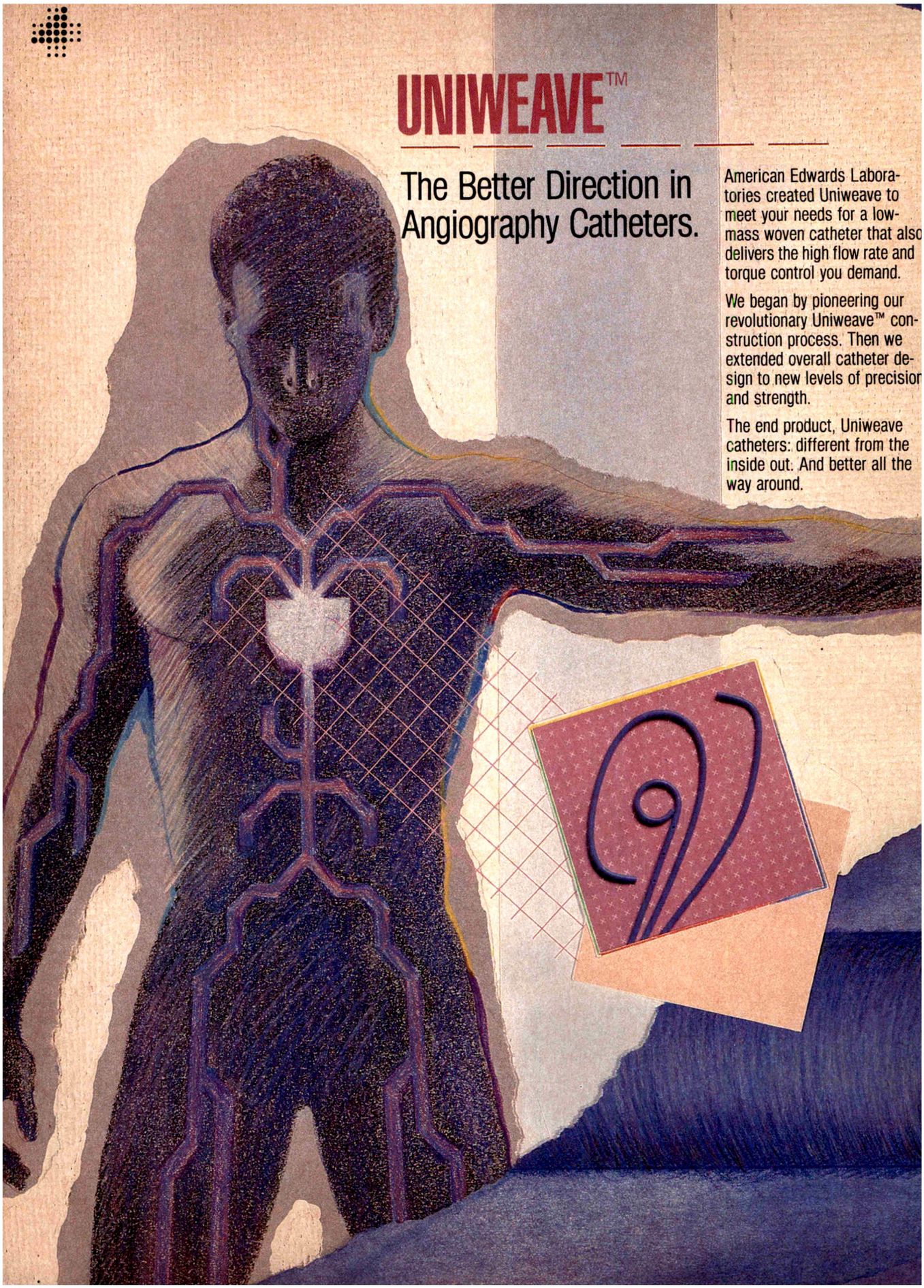
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The Better Direction in Angiography Catheters.
American Edwards Laboratories created Uniweave to meet your needs for a low-mass woven catheter that also delivers the high flow rate and torque control you demand.
We began by pioneering our revolutionary Uniweave™ construction process. Then we extended overall catheter design to new levels of precision and strength.
The end product, Uniweave catheters: different from the inside out. And better all the way around.

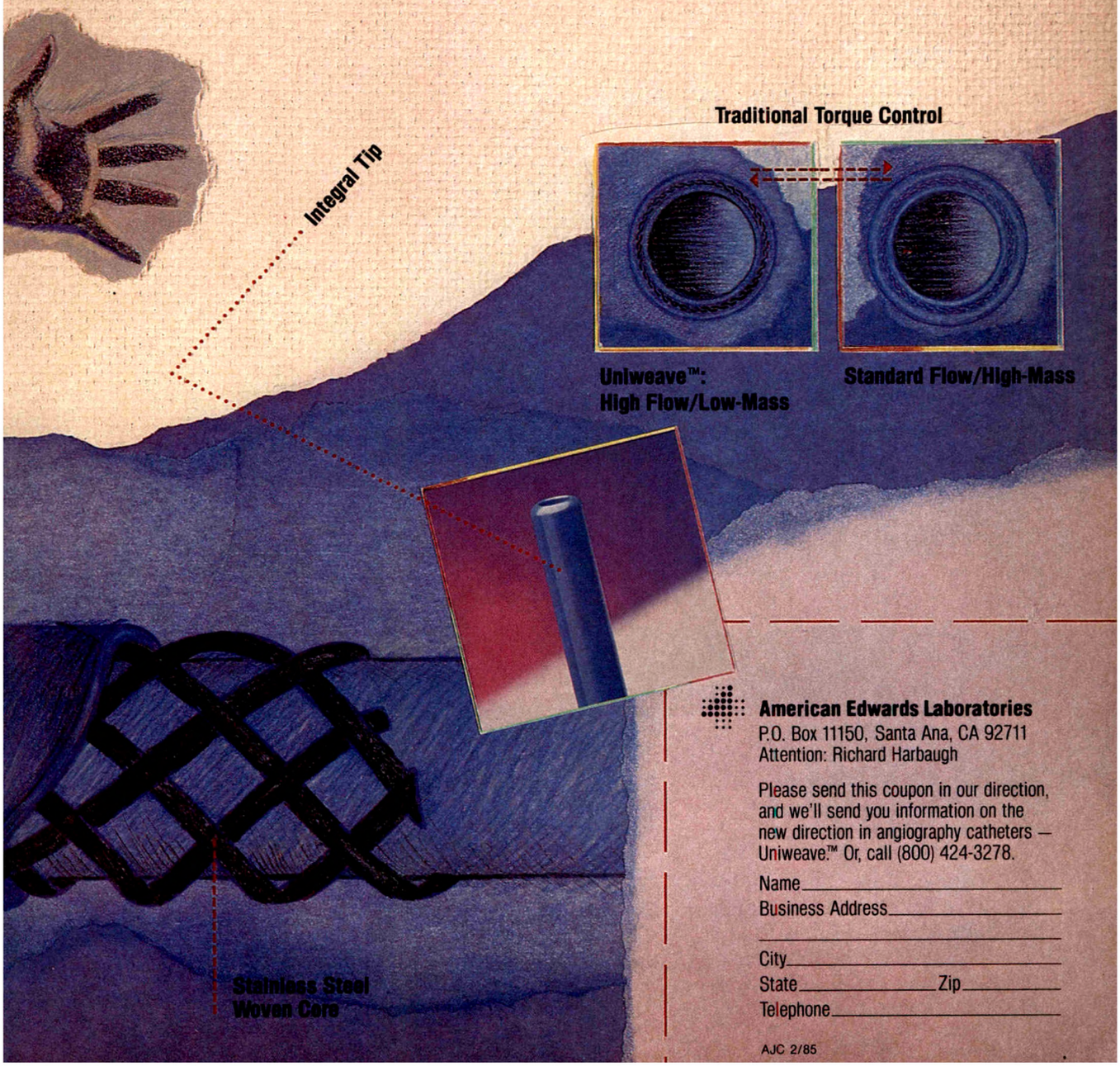
Uniweave. The better direction in construction.
Uniweave construction makes the stainless steel woven core an integral part of the polyethylene catheter wall. The result is enhanced wall strength with traditional control in a smaller French size catheter.

Unibody design. The better direction in patient safety.
Thanks to Uniweave construction, the tip of the catheter is also an integral part of the catheter wall. So, unlike the two-piece welded-on separate tips of competitive catheters, a Uniweave tip can never come off. Uniweave tips also have an unsurpassed shape consistency.

The better direction in high flow through a low-mass catheter.
The inside dimension of a catheter determines potential flow rate. The outside dimension dictates the access size.

Uniweave delivers the flow you need through an exceptionally strong, low-mass catheter.

The first step in the future direction of angiography.
We believe Uniweave angiography catheters will bring the option of out-patient angiography a step closer to reality. Our low-mass design means Uniweave requires a smaller access site — decreasing the possibilities of post-procedural bleeding.



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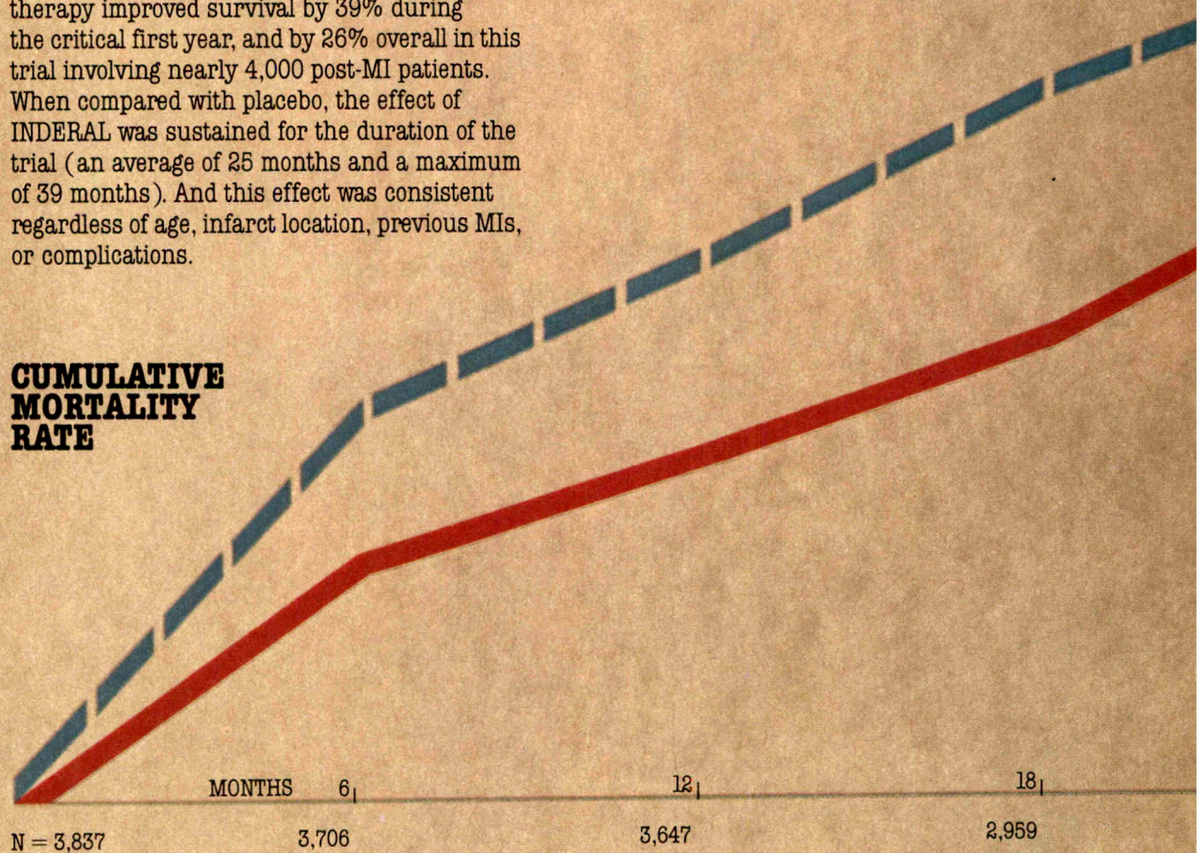
AJC 2/85

INDERAL® (PROPRANOLOL HCl) MAKES A CRITICAL DIFFERENCE, POST-MI

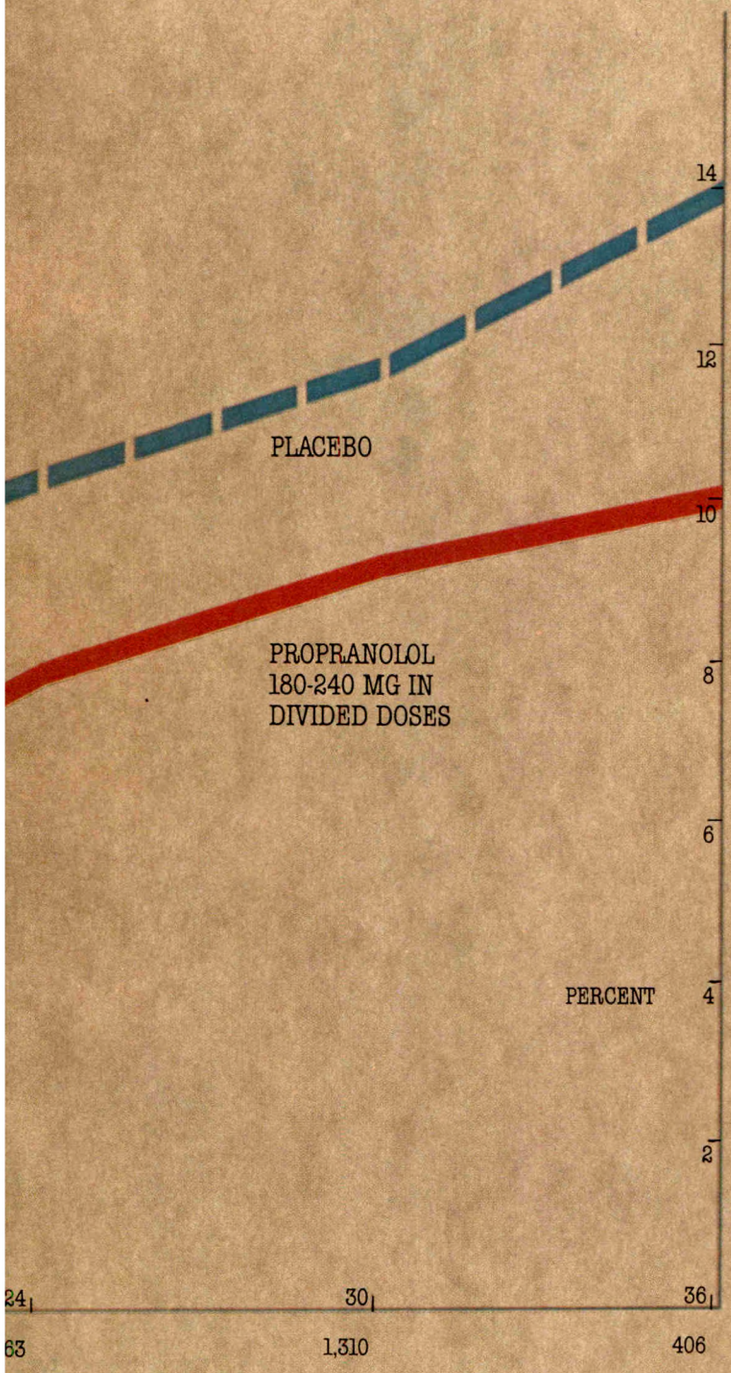
THE AMERICAN HEART ATTACK TRIAL PROVES INDERAL HAS THE POTENTIAL TO SAVE LIVES*

INDERAL significantly improves post-MI survival. This has not been proven for all beta blockers.

Only INDERAL has proven, in a major U.S. heart attack trial, that it can save lives. INDERAL therapy improved survival by 39% during the critical first year, and by 26% overall in this trial involving nearly 4,000 post-MI patients. When compared with placebo, the effect of INDERAL was sustained for the duration of the trial (an average of 25 months and a maximum of 39 months). And this effect was consistent regardless of age, infarct location, previous MIs, or complications.



*All study findings are excerpted from β-Blocker Heart Attack Trial Research Group: A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247:1707-1714.



WITH ITS FAVORABLE SIDE EFFECTS PROFILE–INVESTIGATORS RECOMMEND INDERAL THERAPY FOR AT LEAST 3 YEARS POST-MI†

The study participants, who represented a wide range of risk categories as seen in today's practice, began therapy 5 to 21 days after the infarction, once clinically stable. The dosage was 180 to 240 mg per day. At this appropriate dosage level, INDERAL was well tolerated even in the high-risk population of patients. Incidence of patient complaints on propranolol was similar to complaints on placebo, and consistent with those generally reported with the use of INDERAL. †INDERAL should not be used in the presence of congestive heart failure, heart block greater than first degree, bronchial asthma, and cardiogenic shock.

INDERAL IS THE ONLY BETA BLOCKER INDICATED FOR HYPERTENSION, ANGINA, ARRHYTHMIA, AND POST-MI

Lifesaving potential that rarely interferes with everyday living...the critical difference that INDERAL makes, post-MI.

INDERAL®
(PROPRANOLOL HCl)

THE POTENTIAL TO SAVE LIVES

10 mg 20 mg 40 mg 60 mg 80 mg 90 mg

The appearance of these tablets is a registered trademark of Ayerst Laboratories.

Please see next page for brief summary of prescribing information.

POST-MI

INDERAL®

(PROPRANOLOL HCl)

THE POTENTIAL TO SAVE LIVES

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U.S. centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure; certain conduction defects; angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol was administered at either 60 or 80 mg t.i.d. based on blood levels achieved during an initial trial of 40 mg t.i.d. Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of INDERAL was consistent regardless of age, sex or site of infarction. Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q.i.d. gave overall results which support the findings in the BHAT.

Although the clinical trials used either t.i.d. or q.i.d. dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b.i.d. dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL: In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d. regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC: Studies in normal volunteers have shown that a 90 mg b.i.d. regimen maintains beta blockade at, or above, the minimum for 60 mg t.i.d. dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, t.i.d. dosing gave more beta blockade than b.i.d. dosing; at 20-24 hours the trend of the relationship was reversed. These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetic).

PHARMACOKINETIC: A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b.i.d. are below those provided by the same daily dosage given t.i.d. at 10-12 hours after the first dose of the day but above those of a t.i.d. regimen at 20-24 hours. However, the blood levels produced by b.i.d. dosing were always equivalent to or above the minimum for t.i.d. dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the b.i.d. regimen was about 17% greater than for the t.i.d. regimen (1,194 *vs.* 1,024 ng/ml• hr).

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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Value of Multiple Echocardiographic Views in the Evaluation of Aortic Stenosis in Adults by Continuous-Wave Doppler

GEORGE A. WILLIAMS, MD, ARTHUR J. LABOVITZ, MD, JEANNE G. NELSON, and HAROLD L. KENNEDY, MD

Fifty-two adults referred for evaluation of aortic stenosis (AS) were studied using continuous-wave and pulsed Doppler echocardiography. Three windows were used to determine which approach (apical, right parasternal or suprasternal) yielded optimal results. Doppler-derived peak aortic valve gradients were compared with the peak gradients measured at cardiac catheterization in 23 patients. High-velocity jets were best recorded from the cardiac apex and less frequently from the right parasternal and suprasternal areas. However, gradients from the right parasternal area correlated best with cardiac catheterization findings, although recordings could be made from this window in only 49% of the patients. Velocities from the suprasternal window were significantly ($p < 0.01$) lower than those from the apex or right parasternal areas. Gradient underestimation from the suprasternal window tended to increase with age of the patient ($p < 0.1$). When the maximal Doppler derived gradient from any window was compared with catheterization measurements, the correlation coefficient was 0.86. Gradients derived from Doppler velocities accurately predicted severe (more than 50 mm Hg) gradients at catheterization. Thus, Doppler echocardiography is useful in evaluation of AS when several windows are used for optimal assessment of aortic valve gradient.

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Doppler echocardiography is a valuable adjunct to the noninvasive evaluation of aortic valve stenosis (AS). Before Doppler techniques were introduced, approaches to AS quantitation using echocardiography[1–3] were limited to describing deformity and calcification. Pulsed Doppler added initial quantitative information through its ability to document and quantitate the extent of disturbed flow distal to the lesion.[4,5] Continuous-wave Doppler allowed measurement of the transvalvular gradient.[6–8] Since not all patients can be examined from any 1 window,[6,9,10] Doppler recordings have been made from multiple windows.[6,8] In young patients the supravalvular windows were the most reliable,[6] but not in older patients.[9,10] We investigated the value of 3 windows (apical, right parasternal and suprasternal notch) in older patients with acquired AS, the relation of age to the adequacy of each window, and the use of all 3 windows in each patient to improve localization and quantitation of abnormal signals.

From the Department of Internal Medicine, Division of Cardiology, St. Louis University School of Medicine, St. Louis, Missouri. Manuscript received July 23, 1984; revised manuscript received November 5, 1984; accepted November 6, 1984.

Address for reprints: George A. Williams, MD, Division of Cardiology, St. Louis University Hospital, 1325 South Grand Boulevard, St. Louis, Missouri 63104

Methods

Between November 1982 and July 1983, 52 patients (30 men, 22 women) referred for AS were examined with Doppler echocardiography. Only patients with echocardiograms that showed aortic valvular thickening or calcific deposits and reduced mobility were selected. Patients with congestive heart failure, moderate to severe aortic regurgitation by physical examination, or more than grade 1/6 aortic regurgitation at catheterization were excluded. The mean age was 63 years (range 20 to 82); 2 patients were 40 years old.

Twenty-three patients had aortic valve gradients detected at cardiac catheterization. Doppler was performed in a blinded fashion within 24 hours after cardiac catheterization in 19 patients, within 1 week before catheterization 3 patients, and at 1 year in a patient with mild congenital AS and no signs of progression of AS.

Doppler technique: The Irex System IIIB or Exemplar were used to record Doppler signals. Pulsed and continuous-wave Doppler were recorded with simultaneous 2-dimensional imaging using a 2.5 or 3.5-MHz imaging and 2.0-MHz Doppler frequency. A 2.0-MHz nonimaging Doppler trans-

ducer was used when weak signals were recorded with simultaneous imaging. Pulsed Doppler was used with simultaneous imaging in an apical 5-chamber view to identify the source of high-velocity signals as being the aortic valve area. Continuous-wave Doppler interrogation of the entire depth of the heart detected the highest possible velocities at each area. Two criteria were used to assess angulation of the Doppler beam with the high-velocity jet in the continuous mode. First, the beam was assumed to be parallel to the high-velocity jet when the velocities were highest on the Doppler spectral tracing. Second, the interrogating beam was assumed to be adequately aligned with the jet when the spectral tracing of the Doppler output revealed a maximal concentration of high velocity signals outlining the tracing with few low velocity signals (Fig. 1) and a clear pitch was heard from the auditory output.

Three windows were evaluated: left ventricular apex at or near the point of maximal impulse, the right parasternal area at the second to fourth interspace, and the suprasternal notch. The aortic transvalvular gradient was estimated by the modified Bernoulli formula[11]: $P = 4(V_2^2 - V_1^2)$, where V_2 represents the jet velocity and V_1 the left ventricular outflow tract velocity. When V_1 is less than 1 m/s, the transvalvular pressure estimate changes less than 4 mm Hg, and the gradient was calculated from the highest velocity from any site as $P = 4(V\ max)^2$. Normal aortic velocities were assumed to represent the lack of a transvalvular gradient.

Cardiac catheterization was performed in 23 patients. Pressure gradients were recorded from fluid-filled endhole catheters using either a slow pullback from left ventricle to aorta or simultaneously from left ventricle and femoral artery through a sidearm sheath. In the latter case, the gradient was corrected for any aortofemoral systolic pressure difference. The peak-to-peak catheterization gradient was compared to the Doppler gradient by linear regression analysis.

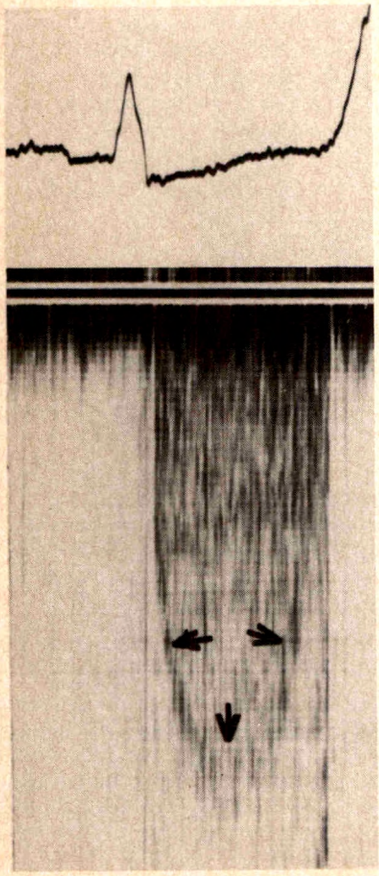

FIGURE 1. Isolated flow velocity profile shows characteristics of an adequately aligned Doppler beam. A high concentration (**dark outline**) of high-velocity reflectors surrounds the trace (**arrows**) with relatively fewer low velocity reflectors within the borders of the tracing.

Results

Technically adequate tracings were obtained from at least 1 viewing window in 51 of 52 patients (98%). Stronger signals and higher velocity tracings were produced by the independent transducer in 47 of the 52 patients (90%). Doppler gradients ranged from 0 to 136 mm Hg.

The apical 5-chamber view was the easiest to record. Aortic jet velocities were recorded in 47 of 52 patients (90%). In 6 patients the velocities could only be recorded from the apex. Calculated gradients from the apex ranged from 0 to 136 mm Hg. In 38 patients, velocities recorded from the apex equaled or exceeded those recorded from the other areas. Left ventricular outflow tract velocities were recorded from the apex in all patients and aortic insufficiency was detected by Doppler in 18 patients (35%). It was clinically unsuspected in 17. In 8 of the patients with aortic insufficiency by Doppler, the diagnosis was confirmed at cardiac catheterization.

The right parasternal view was the most difficult to record, requiring angulation of the transducer from the third, fourth or fifth intercostal spaces to adequately record high-velocity jets. Appropriately oriented jet recordings were possible in 25 of the patients (49%). Right parasternal area velocities were the highest recorded from any window in 6 patients and equaled maximal velocities from other areas in 3 other patients. In 1 study the right parasternal area was the only view available.

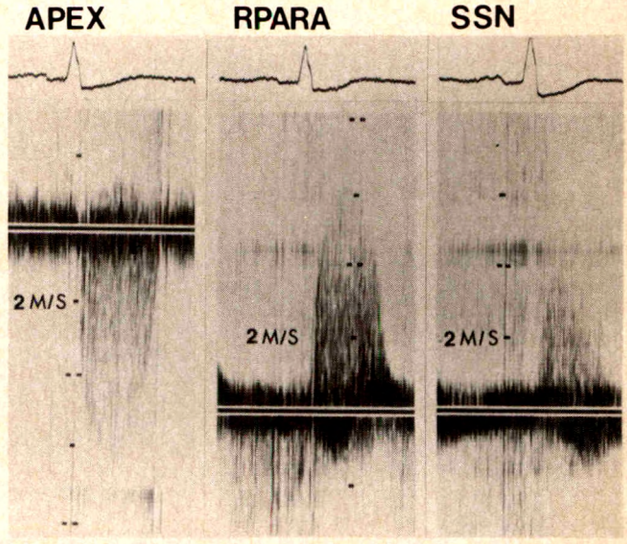

FIGURE 2. Doppler recordings from 3 areas in 1 patient. The profile at the apex reveals a sharp border and a peak velocity of 6.0 m/s. At the right parasternal area (RPARA), a similar velocity is seen but the outline is less well defined. At the suprasternal notch (SSN), a lower velocity and less well defined outline are present.

Suprasternal notch blood flow recordings could be made in 35 of the patients (69%). In 2 cases the suprasternal notch was the only view that could be recorded. Measured velocities were usually lower than those from the other 2 areas, being equal to or greater than the velocities from the other areas in only 4 of 51 patients (8%).

Representative tracings from each area are shown in Figure 2. The apical velocity curve reveals a well outlined tracing with a maximal velocity of approximately 6 m/s. A similar velocity is seen from the right parasternal area; however, the outline is less well defined than that of the apical tracing. The suprasternal notch tracing lacks a well defined outline and the measured velocity is lower than that seen from the other 2 areas. Velocities from the apex (3.6 ± 1.1 m/s) and right parasternal area (3.5 ± 1.0 m/s) were similar (Fig. 3). Suprasternal notch velocities (2.3 ± 0.9 m/s) were significantly ($p < 0.001$) lower than those of the other 2 areas.

The underestimation of aortic velocity from the suprasternal notch tended to increase with age. When suprasternal notch velocities were compared with maximal velocity the mean underestimation was 19% in patients between 40 and 60 and 31% in those over 60 years old ($p < 0.1$).

Catheterization-Doppler correlation: Aortic valve gradients at catheterization ranged from 0 to 125 mm Hg. The correlation between catheterization and Doppler gradients was good (Fig. 4). In 1 patient, despite an adequate tracing, the catheterization gradient was underestimated by 66 mm Hg (74 vs 140 mm Hg).

When a 50-mm Hg gradient was used to separate severe from less severe AS, Doppler accurately identified 11 of 12 patients with gradients less than 50 mm Hg. There were no patients who had a catheterization gradient greater than 50 mm Hg classified as having a lower gradient by Doppler.

In 10 of the 12 patients with catheterization gradient less than 50 mm Hg Doppler overestimated the gradient by 2 to 25 mm Hg (mean 10). Examination of instantaneous gradients in the patient with the greatest disparity revealed the maximal instantaneous Doppler gradient (36 mm) at 200 ms after the QRS, and the peak to peak gradient from catheterization (20 mm) at 320 ms after the QRS. As a result, a disparity of 16 mm Hg was present between the maximal instantaneous Doppler gradient and peak to peak pressure gradient.

Twenty-one patients who underwent catheterization had adequate recordings from the left ventricular apex, with a correlation value of 0.88 between calculated and catheterization gradients (Fig. 5). Only 9 patients could be examined from the right parasternal area. The Doppler results closely correlated with catheterization results ($r = 0.93$). At the suprasternal notch, patients had adequate tracings. In 3 of the 15 the gradient was underestimated by 10 mm Hg or more compared with catheterization ($r = 0.79$).

Discussion

The use of Doppler ultrasound to quantitatively evaluate AS gradients requires proper sampling and recording technique and the ability to record high velocity flows accurately. In this study continuous-wave Doppler provided several advantages. Continuous-wave Doppler accurately measured high velocity. Scanning along the entire depth of the interrogating beam can improve localization of abnormal jets.[12] The accuracy of the Doppler technique depends on the ability to orient the sound beam parallel to the jet. Using continuous-wave Doppler and spectral tracings allowed estimation of the orientation of the jet and ultrasonic beam[7] by the presence of a higher-pitched audio signal and concentration of reflector density at the top of the spectral trace. This ability is particularly important in acquired AS. Under ideal conditions flow is assumed to be parallel to vessel walls and angle correction can be made visually. In a straight tube model, turbulent post–jet flow disturbance and distal relaminarization of flow have been demonstrated.[13] Although the jet may be parallel to vessel walls as in the straight tube model, in acquired AS the high-velocity jet is often eccentric because of valve deformity. As a result, it is important to estimate the angle of incidence of the jet and sound beam from the Doppler characteristics.

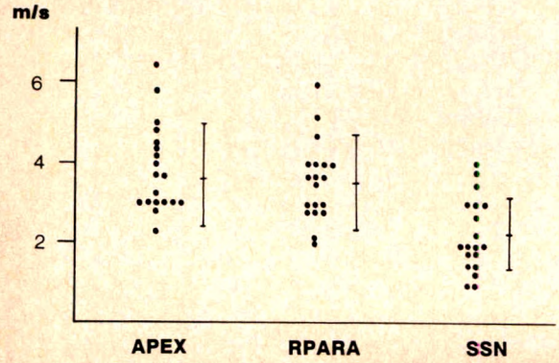

FIGURE 3. The maximal velocities from the apex, right parasternal area (RPARA), and suprasternal notch (SSN) for 19 patients.

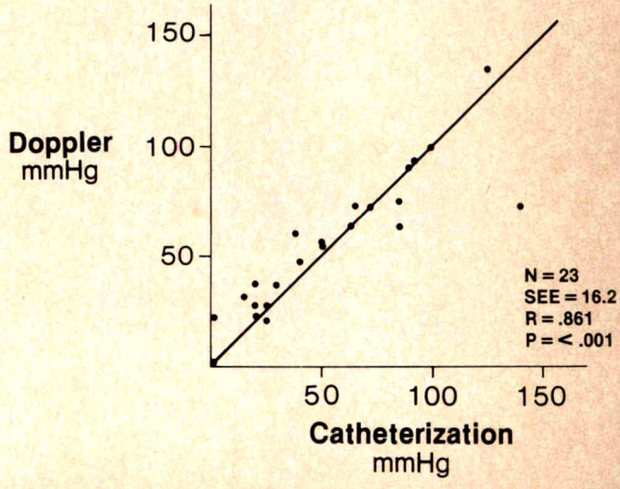

FIGURE 4. Aortic peak gradient obtained at cardiac catheterization and that calculated from Doppler tracing in 23 patients. In 22 patients a close relation to the line of identity is present. In 1 patient a significant underestimation occurs, possibly secondary to angulation.

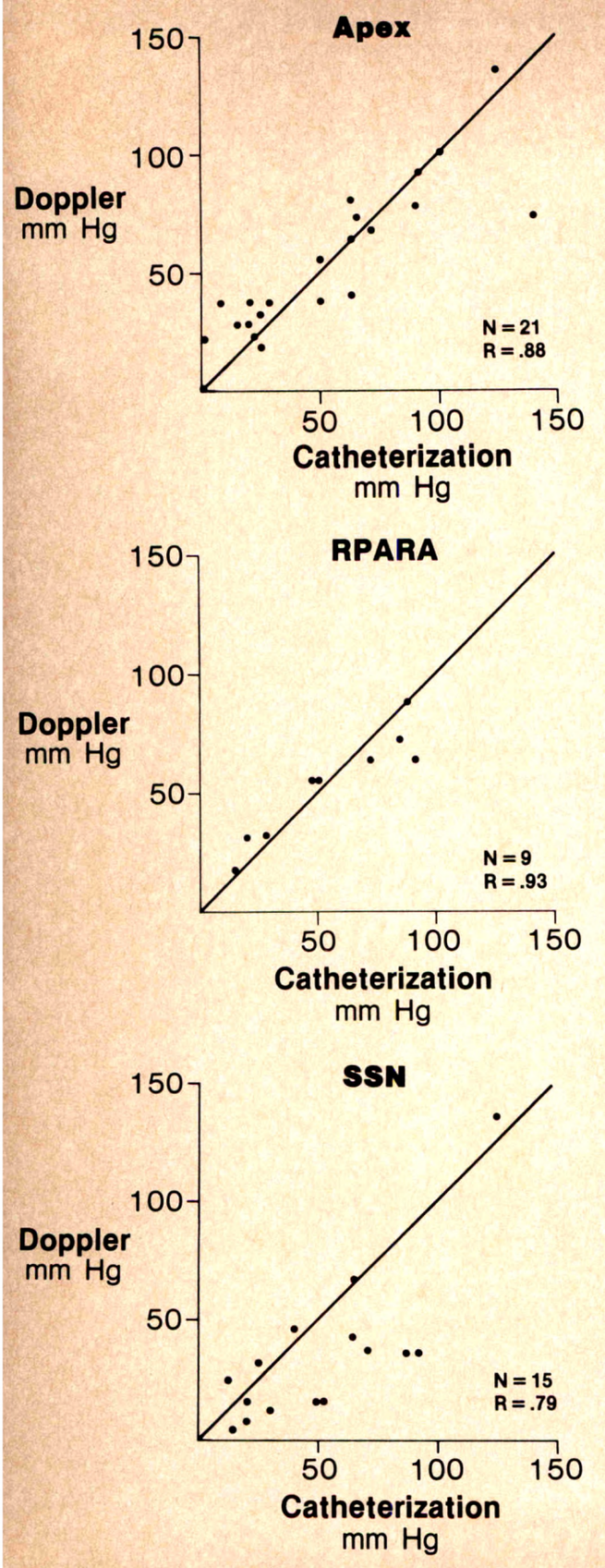

FIGURE 5. Comparison of catheterization gradient with Doppler calculated gradient obtained from each area. The correlation was 0.88 for the cardiac apex (**top**), 0.93 for the right parasternal area (RPARA) (**middle**) and 0.79 for the suprasternal notch (SSN) (**bottom**).

Continuous-wave Doppler cannot localize the site of obstruction, showing all velocities along the interrogating beam. Thus, pulsed Doppler with simultaneous imaging was used to localize the jet to the aortic valve.

The use of multiple sampling sites has been recommended,[6,7] but the reliability of multiple sites has not been compared in adults. In a group of younger patients with valvular AS,[6] the supravalvular areas provided better correlation with measured gradients than the apical area. Similar results were found by Stamm and Martin.[8] Others[9,10] have used only supravalvular views for evaluating AS. These studies, using a combination of suprasternal and right or left parasternal areas, found correlation with catheter gradients of 0.85 and 0.86 respectively. However, in one of the studies[10] 2 patients with catheterization gradients greater than 50 mm Hg were not recognized by Doppler and 4 of 35 patients had inadequate signals from these windows. In the present study, 51 of 52 patients (98%) had adequate tracings. The right parasternal area provided calculated gradients closest to those of cardiac catheterization, as in the study of Hatle,[6] but the low success rate of recording velocities at this site (49%) is similar to others.[7] In this study the suprasternal notch view, although easier to record than the right parasternal area, had significantly lower ($p < 0.001$) recorded velocities. The most likely explanation for this finding lies in the ages of our patients. Only 7 patients were younger than 60 years; the rest were 60 to 82 years old. Underestimation tended to increase with age in this group, although not enough patients under 60 years old were present to achieve statistical significance. Although the continuous-wave Doppler can penetrate to the aortic valve level, the jet from the valve may be oriented at an angle to the Doppler beam due to valve deformity and ectasia of the aorta present in older patients. Since the Doppler shift is inversely proportional to the cosine of the angle of the intercept of the flow vector and the beam, the resultant calculated velocity will be lower. In the present study the Doppler signals were most readily obtained from the apex and tended to produce velocities equal to or higher than those from the other views. The apical view also allowed scanning of the left ventricular outflow tract with pulsed Doppler to localize the site of obstruction.[4]

In our cases of mild AS with normal left ventricles, overestimation of the valve gradient was present in 10 of 12 patients. Although the mean overestimation was low, in 4 patients it exceeded 10 mm Hg. The explanation for this overestimation lies in the difference of measurement technique between echocardiography and catheterization. Doppler jet velocities estimate the maximal instantaneous pressure difference between the left ventricle and aorta, which occurs early in systole in mild AS. The peak-to-peak pressure gradient drop measured at catheterization occurs later in systole and is lower than the maximal systolic gradient.

The major impact of our findings is that hemodynamically important AS (pressure drop more than 50 mm Hg) can be separated from less severe stenosis in 98% of patients when 3 windows are used. All patients in this study had normal left ventricular function by

2-dimensional echocardiography. Doppler pressure gradients must be interpreted taking into account left ventricular function. The jet velocities are related only to the pressure gradient, and both pressure and velocity decrease with left ventricular failure.

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Coronary Artery Luminal Diameter in Aortic Stenosis

SULTAN A. ABDULALI, MD, B. GANESH BALIGA, MD,
ANDREW D. CLAYDEN, BS, PhD, LIMA,
and DONALD R. SMITH, MD

The coronary artery luminal diameters in 32 patients with aortic stenosis (AS) were compared with those of 24 control subjects without left ventricular (LV) hypertrophy by means of a derived index. Patients with AS had significantly larger coronary arteries than the control subjects ($p < 0.01$). The increase in coronary luminal diameter had a weak correlation to LV wall thickness ($r = 0.32$) and LV mass ($r = 0.34$). Among 21 patients with AS and normal coronary angiograms, those with angina had higher peak LV pressures (224 ± 8 vs 196 ± 7 mm Hg) and greater peak systolic gradients (103 ± 9 vs 74 ± 10 mm Hg) than those without angina ($p < 0.05$). However, there was no significant difference in coronary artery diameters, peak LV stress or LV tension at rest between patients with and without angina.

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Patients with aortic stenosis (AS) have as much as a 3-fold increase in left ventricular (LV) mass.[1] Physiologic studies in patients with AS have shown that at rest, blood flow per gram in the left ventricle is normal.[2–4] To maintain this normal flow to the hypertrophied left ventricle, coronary artery size must increase concomitantly. Inadequate growth of the large epicardial vessels in hearts with severe LV hypertrophy has been reported.[5,6] Marcus et al[7] speculated that inadequate growth of the microcirculation may be the mechanism of the reduced coronary reserve in patients with AS and angina who do not have coronary artery disease.[7] This study examines coronary arterial size during LV coronary and angiography in patients with AS and LV hypertrophy compared with that in "normal" control subjects and assesses whether coronary artery size correlates with any LV hemodynamic measurements or with the presence or absence of angina in the absence of coronary artery disease.

Methods

Patients: The cardiac catheterization data and LV coronary angiograms of all patients with pure AS investigated in our department from 1979 through 1983 were reviewed. Thirty-two patients who had satisfactory angiograms that allowed accurate measurement of LV variables and coronary artery size were identified. Their clinical notes were then reviewed and they were subclassified according to the presence or absence of angina pectoris. Twenty patients had a history of angina (Table I).

The 24 patients in the control group were investigated for atypical chest pain and had normal coronary angiograms. They had normal electrocardiograms at rest and negative or indeterminate exercise tests. They were diagnosed as having noncardiac chest pain (Table I).

Cardiac catheterization technique: All treatment was stopped 12 hours before the examination. After an overnight fast, 10 mg of diazepam was administered orally as premedication. Standard left-sided (and right-sided, if necessary) cardiac catheterization was carried out in the supine position. All patients with AS underwent LV catheterization by the transseptal route. The LV angiogram was performed in the right anterior oblique projection using 50 ml of Urografin-370® injected by a pump at a rate of 12 ml/s. Coronary arteriograms were performed by the Judkins technique using 10 to 12 ml of the same contrast given by hand injection for each projection. An 8Fr gauge catheter was used for right and left coronary arteries for all coronary angiograms. A cine film strip of an area determination grid (Namic) was routinely taken at the end of each investigation at the estimated distance of the left ventricle (10 cm above the table) from the camera for each patient.

Determination of coronary artery luminal index and left ventricular variables: The index of coronary luminal diameter was determined as follows. The coronary angiogram was projected on to a white screen and the presence or absence of any coronary artery narrowing was noted. Severity of any stenosis was assessed visually. Significant disease was defined as luminal narrowing of a major vessel by 70% or more in any projection. Frames of the angiogram that showed clearly the

From the Departments of Cardiology, General Infirmary, and Department of Community Medicine, University of Leeds, Leeds, England. Manuscript received May 14, 1984; revised manuscript received September 18, 1984, accepted September 21, 1984.

Address for reprints: Donald R. Smith, MD, Consultant Cardiologist, The General Infirmary, Great George Street, Leeds LS1 3EX, England.

TABLE I Clinical Data

	Control Group	Aortic Stenosis	
		With Angina	Without Angina
Males	13	16	10
Females	11	4	2
Total	24	20	12
Mean age (yr)	45 ± 10	57 ± 7.5	52 ± 10
No. with CAD	0	9 (45%)	2 (16%)

Values are mean ± standard deviation.
CAD = coronary artery disease.

coronary catheter together with the major coronary arteries (left anterior descending, the left circumflex and right coronary arteries) in end-diastole were identified and used for measurements. With a mathematical caliper the diameter of each of the major coronary arteries was measured in millimeters immediately after their origin and before any further branches had been given off. Measurements were made in 3 projections for the 2 left coronary artery branches and in 2 projections for the right coronary artery. In each projection the diameter of the shaft of the coronary catheter was similarly measured at a point immediately before the beginning of the tapering of the tip. The index of coronary luminal diameters was determined by taking the mean value of the ratios of coronary artery diameter to that of the catheter. As the same size catheter (8Fr) was used in all patients, the index derived in this way discounts variation in magnification between patients and projections, allowing comparison of the coronary luminal diameter between groups.

The LV angiograms were projected on a white sheet of paper and the cardiac cycle for volume and mass determination selected. Care was taken to avoid a cycle that occurred during or after an extrasystole. The LV outline was traced at end-systole and end-diastole. The LV wall thickness measurement was made at end-diastole at a point midway between the aortic valve and the apex. The film strip of the area determination grid (which was 1-cm^2 grid marks) was projected over the LV trace to obtain the correction factor for magnification. A graphics analyzer, model 1239 (Numonics), was used to measure LV volumes and wall thickness for the derivation of LV mass. This uses the area-length method described by Dodge[8] for the right anterior oblique projection (regression equation: $V' = 81V + 1.9$).

Peak LV equatorial wall stress was calculated using the thick wall ellipsoid formula of Falsetti et al,[9] which assumes uniform distribution of stress across the LV wall and peak LV tension by the method of Sandler and Dodge.[10]

Certain assumptions are made in the aforementioned calculations: The LV volume and mass calculations are based on the 1-plane data of Sandler and Dodge[11] which assumes the left ventricle to be an ellipsoid, thin-walled shell. The end-diastolic dimensions were used to measure peak LV wall stress. This assumes that dimensions do not change from end-diastole to peak stress and that maximal tensions occurred at time of peak LV pressure.[12] All groups were treated similarly; thus, the conditions should be valid.

Tests for statistical significance used in the analysis were the Wilcoxon test for unmatched data and the Pearson correlation coefficient.

Results

Eleven of the 32 patients (34%) with AS had significant coronary artery disease by angiography. Two of the patients (18%) with coronary artery disease gave no history of angina. All patients were in sinus rhythm.

Patients with AS had higher voltage in the LV leads of the electrocardiograph ($p < 0.01$), higher LV mass ($p < 0.01$), thicker LV walls ($p < 0.01$) and greater end-diastolic volumes ($p < 0.05$) than control subjects (Table II). There were no significant differences in ejection fractions between the 2 groups. The ejection fraction had a significant negative correlation with LV mass ($r = -0.52$, $p < 0.01$). Patients with AS had larger coronary arteries than control subjects (Fig. 1). There was weak correlation between coronary artery luminal diameter index and LV mass ($r = 0.34$). This also applied to the size of the left anterior descending artery when correlated with LV wall thickness ($r = 0.32$).

Patients with aortic stenosis and normal coronary arteries: There was no significant difference in coronary artery size between those with (11 patients) and those without angina (10 patients) (Fig. 2). Patients with angina had higher peak systolic gradients and peak LV pressure ($p < 0.05$). Other measurements, such as ejection fraction, LV end-diastolic pressure, LV end-diastolic volumes, LV mass, wall thickness, peak LV

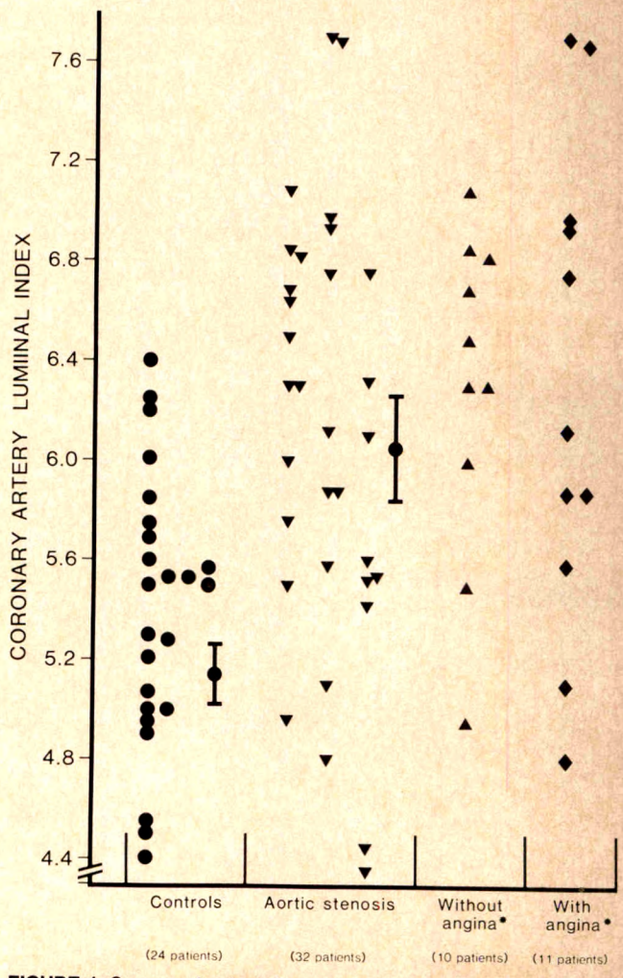

FIGURE 1. Coronary luminal diameter index in control subjects (5.14 ± 0.11) and in patients with aortic stenosis (6.08 ± 0.15). Values are mean ± standard error of the mean. * The 2 columns on the **right** show distribution of patients with aortic stenosis and normal coronary arteries.

TABLE II Left Ventricular Measurement in Control Subjects and Patients with Aortic Stenosis

	Controls (24 pt)	Aortic Stenosis (32 pt)	p Value
ECG voltage—leads $V_1 + V_5$ (mV)	21 ± 6	40 ± 11	<0.01
Peak systolic gradient (mm Hg)		81 ± 33	NA
LV end-diastolic pressure (mm Hg)	9 ± 4	18 ± 8	<0.01
End-diastolic volume (ml)	92 ± 20	115 ± 33	<0.05
Ejection fraction (%)	78 ± 8	74 ± 12	NS
LV wall thickness (mm)	9 ± 2	11 ± 3	<0.01
LV mass/BSA (g/m^2)	91 ± 31	122 ± 51	<0.01
Coronary luminal index			
3 vessels	5.1 ± 0.5	6.1 ± 0.8	<0.01
LAD + circumflex	3.6 ± 0.4	4.2 ± 0.8	<0.01
LAD	1.9 ± 0.2	2.2 ± 0.3	<0.01

Values are mean ± standard deviation.
BSA = body surface area; ECG = electrocardiographic; LV = left ventricular; LAD = left anterior descending coronary artery; NS = not significant; NA = not applicable.

stress and maximal LV tension, were not significantly different between the 2 groups (Table III).

Patients with angina and coronary artery disease had a significantly lower peak systolic gradient (69 ± 10 mm) than those with angina and without coronary artery disease (103 ± 9 mm) ($p < 0.05$).

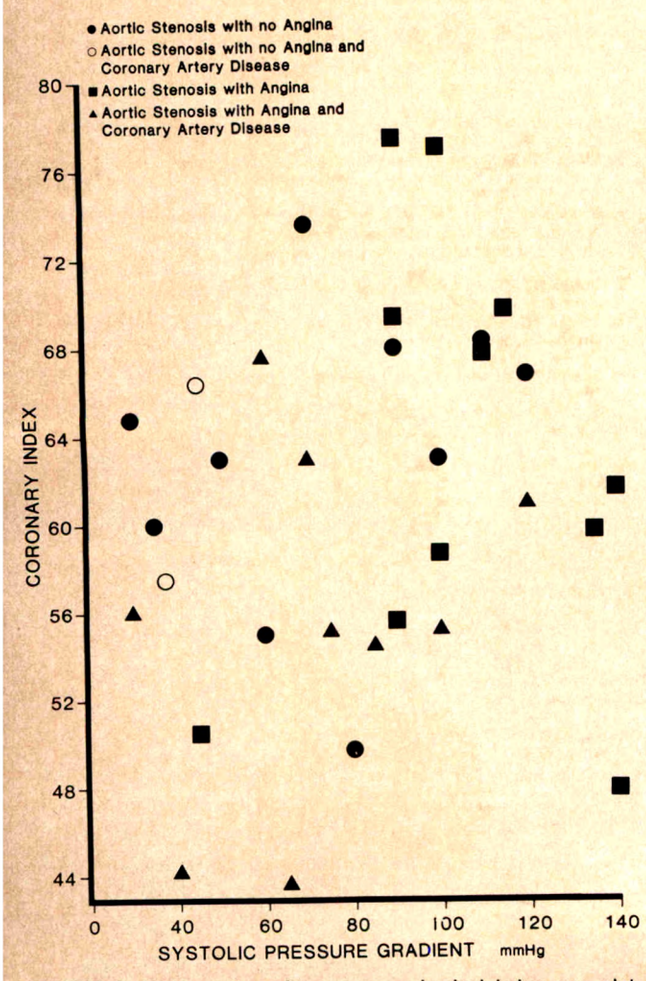

FIGURE 2. Wide scatter when coronary luminal index was plotted against the systolic pressure gradient in patients with aortic stenosis.

Discussion

The mechanism of angina in patients with AS and normal coronary arteries has not been defined. An imbalance between coronary blood flow and the metabolic demand for oxygen in the hypertrophied left ventricle must exist.

Hemostatic mechanisms govern the regulation of phasic coronary flow. An anatomic limitation in blood supply as a result of inadequate growth of coronary vasculature, in response to the increase in LV mass in left ventricular hypertrophy, has been proposed as a mechanism of angina in these patients who do not have coronary artery disease.[5,7,14] Based on postmortem measurements of coronary ostial and epicardial vessel size, it was proposed that the limitation in growth of the large coronary vessels resulted in outstripping of the blood supply to the hypertrophied myocardium causing ischemia.[5,13,14] Our study shows that there is no difference in the size of epicardial vessels in patients with and those without angina and that, in the living subject, there is poor correlation between coronary artery size and LV mass or wall thickness, despite a significant increase in luminal diameter with myocardial hypertrophy.

Studies after stress induced by isoproterenol,[3] atrial pacing[4] and coronary occlusion[7] all show that patients with AS and angina who do not have coronary artery disease have a greater reduction in coronary reserve than those without angina and without coronary artery disease. Impaired vasodilator responses in response to exercise have been demonstrated in animals with LV hypertrophy.[15,16] Epicardial vessels contribute minimally to coronary vascular resistance[17] and are unlikely to be responsible for these vasodilator responses. However, if the growth of coronary microcirculation in the hypertrophied left ventricle did not keep pace with the increase in LV mass in the presence of normal flow, minimal coronary vascular resistance would increase and, thus, limit coronary vasodilator responses in the hypertrophied ventricle.[7,15] At rest, there was no ob-

TABLE III Left Ventricular Measurements in Patients with Aortic Stenosis and Normal Coronary Arteries

	Aortic Stenosis		
	With Angina (11 pt)	Without Angina (10 pt)	p Value
Peak systolic gradient (mm Hg)	103 ± 29	74 ± 32	<0.05
Peak LV systolic pressure (mm Hg)	224 ± 26	196 ± 22	<0.05
LV end-diastolic pressure (mm Hg)	19 ± 10	15 ± 5.0	NS
End-diastolic volume (ml)	112 ± 26	113 ± 55	NS
Ejection fraction (%)	77 ± 10	70 ± 16	NS
LV wall thickness (mm)	11.7 ± 4	10.3 ± 2	NS
LV mass/m^2 (g/m^2)	122 ± 55	122 ± 66	NS
LV stress ($dynes/cm^2 \cdot 10^3$)	384 ± 119	414 ± 101	NS
LV tension ($dynes/cm \cdot 10^3$)	447 ± 93	433± 136	NS
Coronary luminal index			
3 vessels	6.3 ± 0.9	6.3 ± 0.6	NS
LAD	2.3 ± 0.6	2.2 ± 0.2	NS
LAD + circumflex	4.2 ± 1	4.4 ± 0.4	NS

Values are mean ± standard deviation.
Abbreviations as in Table II.

served difference in our patient with regard to the size of the large coronary arteries in AS patients with and without angina. Do the small resistance vessels behave differently? We argue that the proposed inadequate growth of the coronary microcirculation probably does not account for the mechanism of angina on its own. Other factors probably play a part. During exercise there is an increase in LV ejection period and a reduction in diastolic period of nutrient flow associated with an increase in heart rate. Our AS patients with angina and normal coronary arteries had higher peak LV pressures and peak systolic gradients than those without angina, a finding reported by others.[18] These greater pressures would result in greater extravascular compression of intramural vessels augmenting any abnormality of coronary flow and restricting vasodilation during exercise in patients with angina.

Myocardial oxygen consumption is determined by contractility[19] and LV wall tension.[20] The former is difficult to measure; the latter is determined by the stress the left ventricle is subjected to. The measurement of both these variables in our AS patients, with and without angina, were not significantly different. This finding is not surprising, however, because these data deal with the left ventricle as a whole rather than the distribution of forces across the LV wall. Differential distribution of intramural forces resulting in redistribution of blood flow from the subendocardium to the subepicardium has been put forward as a likely contributor to angina in AS.[3,4,21] This finding is supported by the fact that the ratio of diastolic pressure-time index to systolic pressure-time index is abnormal during exercise in the presence of normal coronary sinus oxygen saturation and coronary sinus blood flow.[21]

Acknowledgment: We thank Anita Vicars for secretarial help and Valerie Binns for help with the statistical analysis.

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Detailed Anatomy of the Normally Functioning Aortic Valve in Hearts of Normal and Increased Weight

MARC A. SILVER, MD, and WILLIAM C. ROBERTS, MD

The area, weight and 4 linear variables were measured in each aortic valve cusp in 100 necropsy patients with normally functioning aortic valves, and the volume of each sinus of Valsalva and the aortic area at the sinotubular junction were determined in the same patients. The sums of the aortic valve cuspal areas, cuspal weights and sinus of Valsalva volumes increased with age ($p < 0.001$) and with heart weight ($p < 0.001$). All 3 variables (cuspal area, cuspal weight and sinus of Valsalva volume) also increased with age and heart weight relative to each other. The luminal area of aorta at the sinotubular junction also increased with age and heart weight and it also increased as the sum of the aortic valve cuspal areas and weights and sinus of Valsalva volumes increased. In only 16% of the 100 patients were the 3 aortic valve cusps of similar size (less than 5% difference in area between cusps); in 51%, 1 cusp was of different size than the other 2, and in 33% of patients all 3 cusps were of different sizes.

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Although various features of dysfunctioning human aortic valves have been described, few reports are available describing results of detailed measurements of normally functioning human aortic valves. This report describes results of measuring at necropsy various dimensions of each aortic valve cusp, the volume of each sinus of Valsalva, and the luminal area of aorta at the sinotubular junction in 100 patients with normally functioning aortic valves.

Definitions

A *normal valve* may be defined as a thin, mobile layer of tissue located in a canal or passage, and this tissue allows free flow through the passageway and prevents reflux of the contents passing by it. When this definition of "valve" is applied to the normal aortic valve, it is applicable only to the 3 cusps (or leaflets). If the 3 aortic valve cusps are excised, an aortic valve is no longer present. Thus, the aortic valve is a structure located between left ventricular outflow tract and the tubular portion of aorta and within the sinus portion of aorta, and it consists of 3 freely mobile cusps. Although they affect both structure and function of the 3 aortic valve cusps, the structures contacted by the aortic valve cusps are not considered part of the aortic valve. The 3 aortic valve cusps are designated right, left and posterior. The term "non-coronary cusp" is best avoided because a coronary artery may originate from the wall of aorta behind the posterior cusp or a coronary ostium may be absent from 1 or both anteriorly located cusps.

A *sinus of Valsalva* is a space that exists between the aortic surface of an aortic valve cusp and the wall of aorta behind that cusp (Fig. 1). It is bounded caudally by the basal attachment of the aortic cusp (to wall of aorta, membraneous or muscular ventricular septum or anterior mitral leaflet) and above by the sinotubular junction. The space serves as a reservoir of blood during ventricular diastole. The *tubular portion of ascending aorta* is that portion beginning at the most cephalad extension of the sinuses of Valsalva and extending to the origin of the innominate artery (Fig. 1).

Methods

During an 18-month period, the measurements described herein were carried out in 100 hearts, which had been fixed in 10% buffered formalin. Death in all 100 patients was either the result of a noncardiac condition or to consequences of atherosclerotic coronary heart disease, a condition that does not affect the aortic valve. Patients with valvular, congenital, pericardial and primary myocardial diseases, patients in whom a cardiac operation had been performed, and patients younger than 18 years of age at death were excluded. If the heart was increased in mass the cause of the cardiomegaly was attributable only to systemic hypertension. Of the 100 patients, 2 were aged 18 to 20 years, 7 aged 21 to 30, 9 aged 31 to 40, 9 aged 41 to 50, 19 aged 51 to 60, 31 aged 61 to 70, 16 aged 71 to 80, 2 aged 81 to 90 and 5 aged 91 to 100 years. The heart weighed less than 400 g in 54 patients and more than 400 g in 46 patients. Of the 61 men, 28 (46%) had hearts less than 400 g and 33 (54%) had hearts more than 400 g; of the 39 women, 26 (67%) had hearts less than 400 g and 13 (33%) had hearts more than 400 g.

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Dr. Silver's present address: Section of Cardiology, Rush-Presbyterian-St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, Illinois 60612. Manuscript received September 12, 1984, accepted October 8, 1984.

Address for reprints: William C. Roberts, MD, Building 10A, Room 3E30, National Institutes of Health, Bethesda, Maryland 20205.

One or more measurements were made in each patient on 6 structures or spaces. Of the 6, one measurement per patient was made in 2: heart weight and area of aortic lumen at the sinotubular junction. Of the other 4 structures or spaces, 3 measurements per patient were made because each patient had 3 aortic valve cusps and 3 sinuses of Valsalva. These 4 structures or spaces were: volume capacity of each sinus of Valsalva; weight of each aortic valve cusp; area of each aortic valve cusp; length of free margin of each cusp (measurement 1 [Fig. 2]); length of attachment margin of each cusp (measurement 2 [Fig. 2]); length from midportion of free margin to midportion of attachment margin (cuspal height) in each cusp (measurement 3 [Fig. 2]); and the straight-line distance between 2 junctions where free margins meet attachment margins of each cusp (cuspal width) (measurement 4 [Fig. 2]). Thus, in the 100 patients, 2,300 measurements of the 6 structures or spaces were possible; of these, 2,146 (93%) were carried out. The heart weight was determined in all 100 patients. The area of the aortic lumen at the level of the sinotubular junction was determined in 75 patients. The capacity of all 3 sinuses of Valsalva was determined in 68 patients or in 204 (68%) of the 300 sinuses. The weight of all 3 cusps individually was determined in 89 patients or in 267 of the 300 separate aortic valve cusps. The area of all 3 cusps was determined in all 100 patients or in all 300 of the possible 300 cusps. All 4 linear measurements (Fig. 2) were performed on each of the 3 aortic valve cusps in all 100 patients, yielding a total of 1,200 measurements of a possible 1,200 measurements.

The heart was weighed after cleaning all 4 cavities of postmortem clot and after excising both the ascending aorta and the pulmonary trunk about 2 cm above the cephalad extension of the semilunar valve cusps.

The volume capacity of each sinus of Valsalva was determined via a 2-ml pipette calibrated into 0.1-ml units. The pipette was filled to its capacity with water. While holding the heart with the sinuses of Valsalva roughly perpendicular to the long axis of the pipette, each sinus was filled to its capacity with water and the amount delivered by the pipette was recorded to the nearest 0.1 ml.

The luminal area of the aorta at the sinotubular junction was determined by incising circumferentially the aorta exteriorly while observing the blade of the knife within the aortic lumen. The thickness of the aortic wall circumferentially at the sinotubular junction was then blackened by a felt-tipped marking pen. The blackened aortic wall was then imprinted on white paper. Tracing paper was then superimposed over the black ring and the inner circumference was traced onto tracing paper. The cross-sectional area (in mm^2) of the aortic lumen then was determined directly by planimetry (KE-compensatory polar planimeter) using a video method described elsewhere.[1] The system was calibrated to 1-cm-square grid (100 mm^2). Each tracing then was placed under a focused camera and the resultant video signal was passed through an electronic integrator and displayed on a television monitor, which ensured that the area being measured was accurate. The analog output voltages of the video planimeters provided on-line measurements of the cross-sectional areas by a digital readout.

The aorta at the level of the aortic valve usually was opened between 2 cusps so that each cusp remained intact. Each of the 3 aortic valve cusps was excised intact along their curved line of attachment (just inside line 2 in Figure 2). Each cusp was then weighed using a Mettler P1210 scale, which has an accuracy to 0.01 g. Then each cusp was flattened (usually simply by applying water) on a sheet of white paper and the attachment margin (measurement 2 [Fig. 2]) and the free margin (measurement 1 [Fig. 2]) was traced onto the paper. The area enclosed by the tracing was measured by videoplanimetry as described above. Measurements 1 to 4 (Fig. 2) were made from the tracing by a flexible plastic metric ruler calibrated in 1-mm units.

Statistical methods: The comparison of means was done using an uncorrelated Student *t* test, and the correlation coefficients were calculated using a Pearson's product moment test. Significance was judged if the test yielded a p value <0.05.

Results

The findings are summarized in Tables I and II and in Figures 3 to 16.

The *sum of the areas of the 3 aortic valve cusps* increased with age (Fig. 3) ($r = 0.40$, $p < 0.001$), with heart weight (Fig. 4) ($r = 0.62$, $p < 0.001$); with total volume of the 3 sinuses of Valsalva (Fig. 5) ($r = 0.61$, $p < 0.001$); with the sum of the weight of the 3 aortic valve cusps (Fig. 6) ($r = 0.77$, $p < 0.001$), and with the aortic area at the sinotubular junction (Fig. 7) ($r = 0.75$, $p < 0.001$).

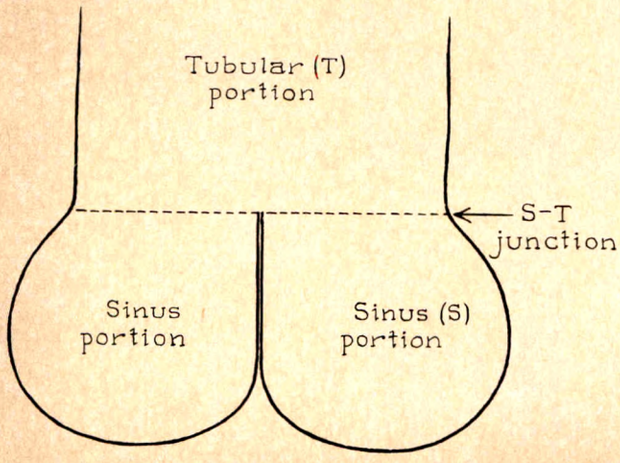

FIGURE 1. Diagram of the sinus and tubular portions of ascending aorta.

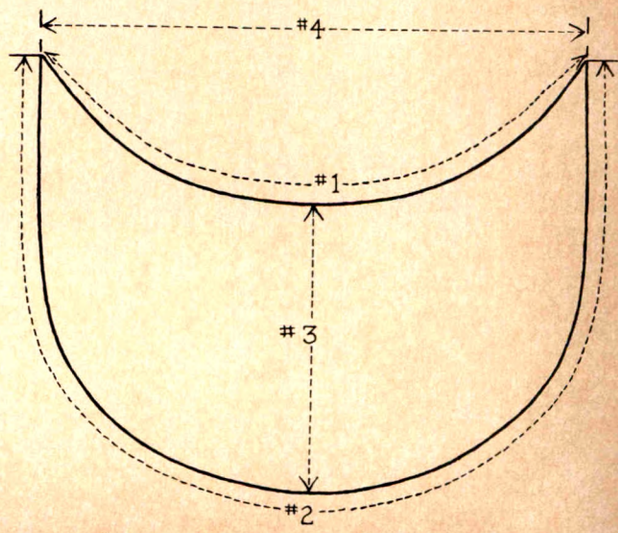

FIGURE 2. Diagram of a single aortic valve cusp illustrating the 4 linear measurements.

TABLE I Summary of Aortic Valve Cuspal and Sinus of Valsalva Measurements in 54 Patients with Normal Sized and in 46 Patients with Enlarged Hearts*

Structure or Space Measured	Cusp or Sinus of Valsalva					
	Right		Left		Posterior	
Heart weight (g)	≤400 (n = 54)	>400 (n = 46)	≤400 (n = 54)	>400 (n = 46)	≤400 (n = 54)	>400 (n = 46)
Area (mm^2)	127–480 (302 ± 77)	266–629 (384 ± 74)	161–456 (300 ± 74)	227–562 (376 ± 70)	162–473 (320 ± 70)	267–614 (381 ± 75)
Sinus volume (ml)	0.4–2.0 (1.0 ± 0.4)	0.8–3.0 (1.4 ± 0.4)	0.4–1.8 (0.9 ± 0.3)	0.6–2.0 (1.2 ± 0.3)	0.4–2.0 (1.1 ± 0.4)	0.6–2.8 (1.4 ± 0.4)
Weight (g)	0.06–0.32 (0.15 ± 0.06)	0.11–0.42 (0.20 ± 0.06)	0.07–0.28 (0.14 ± 0.05)	0.09–0.47 (0.21 ± 0.06)	0.07–0.32 (0.18 ± 0.06)	0.10–0.46 (0.22 ± 0.06)
Free margin (mm) (#1)	21–40 (31 ± 4)	27–46 (34 ± 4)	20–36 (29 ± 4)	25–49 (33 ± 5)	21–35 (30 ± 4)	25–45 (34 ± 4)
Attachment margin (mm) (#2)	32–60 (46 ± 6)	41–71 (51 ± 6)	33–60 (46 ± 7)	40–71 (50 ± 6)	35–60 (47 ± 6)	42–67 (50 ± 5)
Height (mm) (#3)	9–18 (13 ± 2)	11–20 (15 ± 2)	11–18 (14 ± 2)	11–20 (15 ± 2)	10–19 (14 ± 2)	12–18 (15 ± 2)
Width (mm) (#4)	19–40 (30 ± 5)	23–43 (34 ± 4)	18–35 (28 ± 4)	24–46 (32 ± 5)	20–35 (30 ± 4)	25– 43 (33 ± 5)

* The differences in all 8 measurements within each of the 3 cusps or sinuses between hearts that weighed 400 g or less and those that weighed more than 400 g were highly significant ($p < 0.01$).

The *sum of the volumes of the 3 sinuses of Valsalva* increased with age (Fig. 8) ($r = 0.52$, $p < 0.001$); with heart weight (Fig. 9) ($r = 0.58$, $p < 0.001$); with the sum of the aortic valve cuspal area (Fig. 5) ($r = 0.61$, $p < 0.001$); with the sum of the weight of each of the 3 aortic valve cusps (Fig. 10) ($r = 0.58$, $p < 0.001$); and with the aortic area at the sinotubular junction (Fig. 11) ($r = 0.63$, $p < 0.001$).

The *sum of the weights of the 3 aortic valve cusps* increased with age (Fig. 12) ($r = 0.40$, $p < 0.001$); with heart weight (Fig. 13) ($r = 0.57$, $p < 0.001$); with the sum of the area of the 3 aortic valve cusps (Fig. 6) ($r = 0.77$, $p < 0.001$); with the sum of the volume of the 3 sinuses of Valsalva (Fig. 8) ($r = 0.52$, $p < 0.001$, and with the aortic area at the sino-tubular junction (Fig. 14) ($r = 0.62$, $p < 0.001$).

The *aortic area at the sinotubular junction* increased with age (Fig. 15) ($r = 0.69$, $p < 0.001$); with heart weight (Fig. 16) ($r = 0.55$, $p < 0.001$); with the sum of the area of the 3 aortic valve cusps (Fig. 7) ($r = 0.75$, $p < 0.001$); with the sum of the volume of the 3 sinuses of Valsalva (Fig. 11) ($r = 0.63$, $p < 0.001$); and with the sum of the weight of the 3 aortic valve cusps (Fig. 14) ($r = 0.62$, $p < 0.001$).

The ranges and means of the aortic valve cuspal and sinus measurements of each of the 3 aortic valve cusps and sinuses of Valsalva in the patients with hearts that weighed 400 g or less in those with hearts that weighed more than 400 g are summarized in Table I. The mean

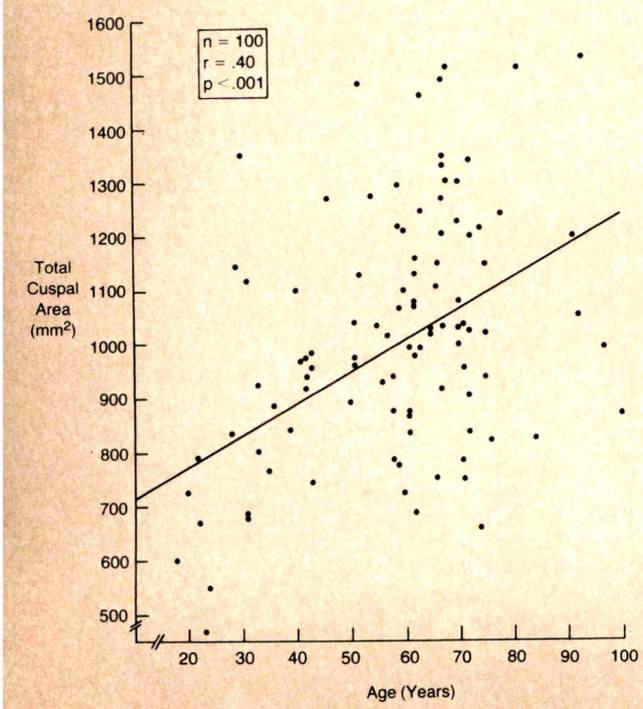

FIGURE 3. Relation of total aortic valve cuspal area to age.

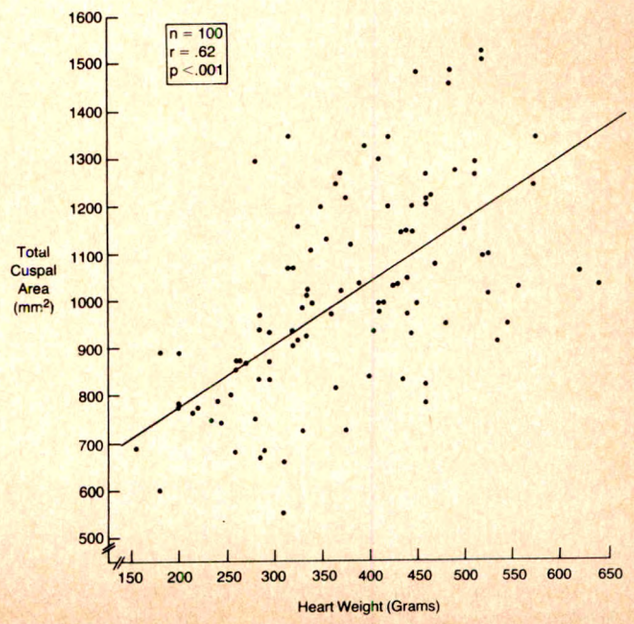

FIGURE 4. Relation of total aortic valve cuspal area to heart weight.

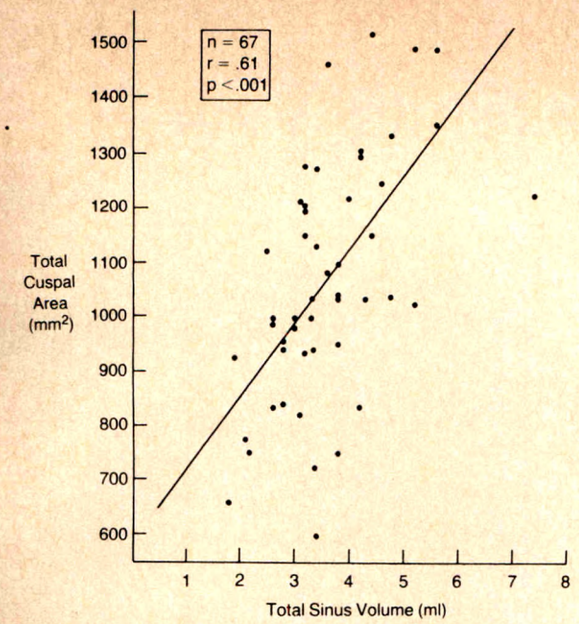

FIGURE 5. Relation of the sum of the 3 aortic valve cusps to the sum of the volumes of the 3 sinuses of Valsalva.

TABLE II Cuspal Differences* in Normally Functioning Aortic Valves in 54 Hearts of Normal Weight and in 46 Hearts of Increased Weight

	Heart Weight (g)		
Cusp Size	≤400	>400	Totals
0 equal-sized cusps (all 3 different)	23 (42.5%)	10 (22%)	33 (33%)
Largest cusp			
Right (R)	4	2	6 (18%)
Left (L)	5	2	7 (21%)
Posterior (P)	14	6	20 (61%)
Smallest cusps			
Right (R)	12	4	16 (49%)
Left (L)	8	4	12 (36%)
Posterior (P)	3	2	5 (15%)
2 equal-sized cusps (1 cusp different)	23 (42.5%)	28 (61%)	51 (51%)
The different cusp			
Right (R)	7	7	14 (28%)
Left (L)	8	9	17 (33%)
Posterior (P)	8	12	20 (39%)
Smaller	13	12	25 (49%)
Larger	10	16	26 (51%)
3 equal-sized cusps (no cusp different)	8 (15%)	8 (17%)	16 (16%)
Total	54 (100%)	46 (100%)	100 (100%)

* Difference more than 5% from the average cuspal area for the 3 cusps of an aortic valve (measured in mm^2).

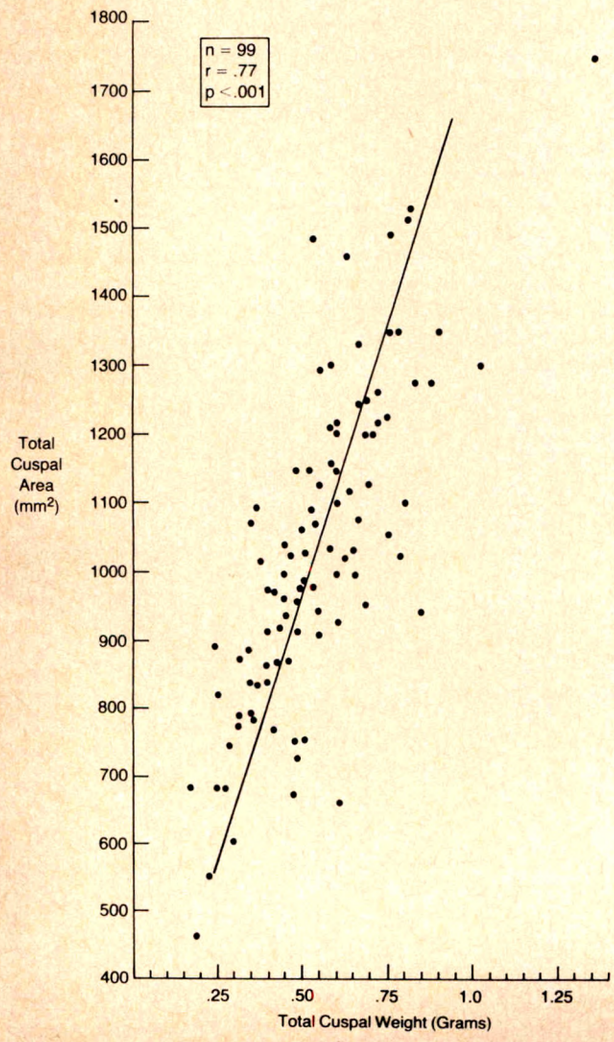

FIGURE 6. Relation of sum of areas of the 3 aortic valve cusps to sum of weights of the 3 aortic valve cusps.

cuspal area, mean cuspal weight, mean sinus of Valsalva volume, and the means of the 4 cuspal linear measurements (numbers 1 to 4 [Fig. 2]) were highly ($p < 0.01$) significantly different for each cusp or sinus in patients with normal sized hearts (≤400 g) compared with the patients with hearts of increased mass (>400 g).

Smaller, insignificant differences occurred in mean sinus of Valsalva volume, and the means of the 4 cuspal

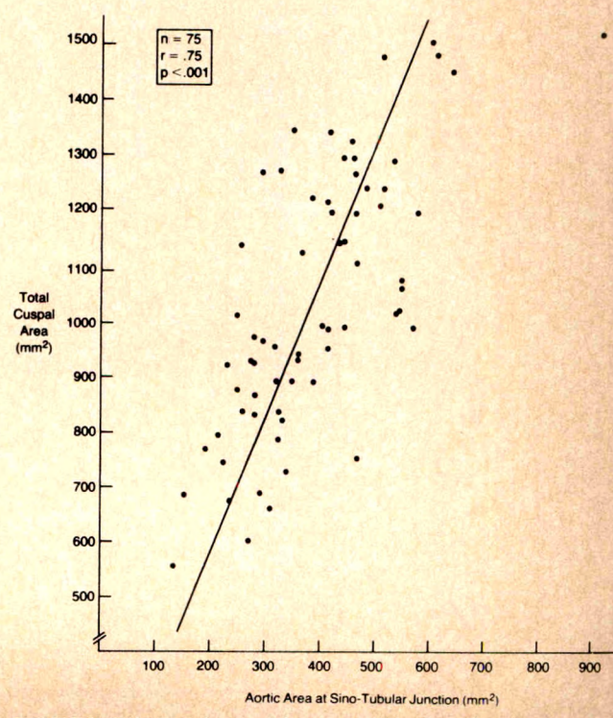

FIGURE 7. Relation of sum of the areas of the 3 aortic valve cusps to aortic area at the sinotubular junction.

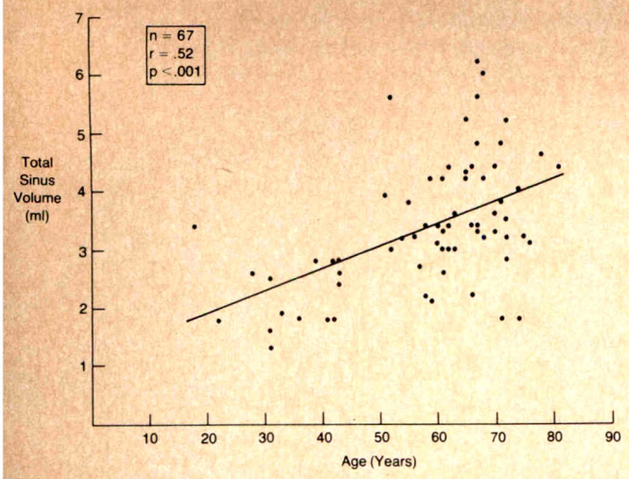

FIGURE 8. Relation of sum of volumes of the 3 sinuses of Valsalva to age.

linear measurements among the 3 cusps or sinuses between the 54 patients with normal-sized hearts (≤400 g) and those with hearts of increased mass (>400 g) (Table I). The posterior cusp, compared to both right and left ones, however, had a larger mean area and mean weight (Table I).

As summarized in Table II, only 16 patients had 3 equal-sized aortic valve cusps; 51 patients had 2 equal-sized cusps (1 different cusp), and 33 patients had no equal-sized cusps (all 3 cusps different). Among the 51 patients with 2 equal-sized cusps, the different-sized cusp was smaller than the other 2 in 25 patients and larger in 26 patients. The different-sized cusp was nearly equally split between the right, left and posterior locations. Of the 33 patients in whom none of the 3 cusps was of equal size, the posterior cusp was the largest in 20, the left in 7 and the right in 6; the posterior

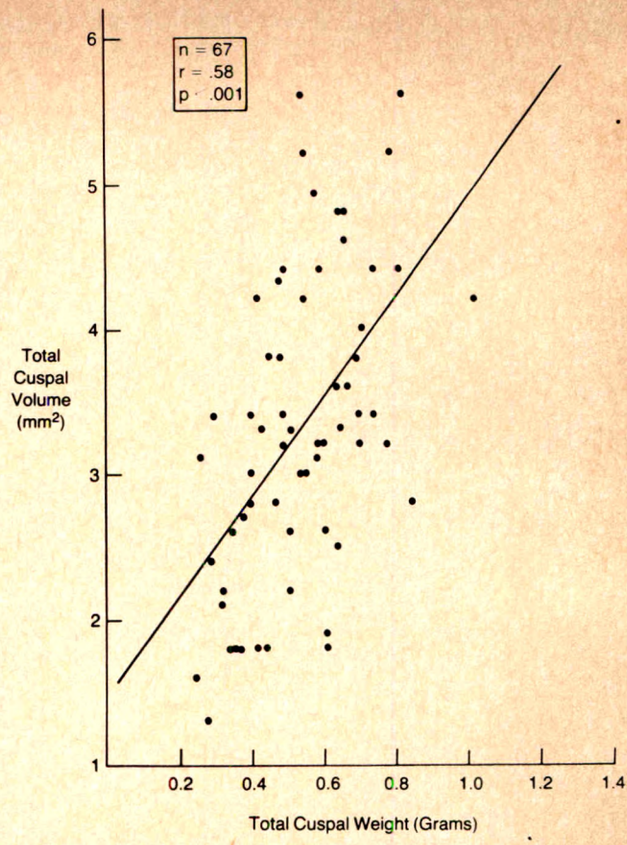

FIGURE 10. Relation of sum of volumes of all 3 sinuses of Valsalva to sum of weights of the 3 aortic valve cusps.

cusp was the smallest in 5, the left in 12 and the right in 16 (Table II).

The luminal area of aorta at the sinotubular junction (measured in 75 patients) ranged from 139 to 915 mm^2 (mean 392 ± 108); the range in the 40 patients with

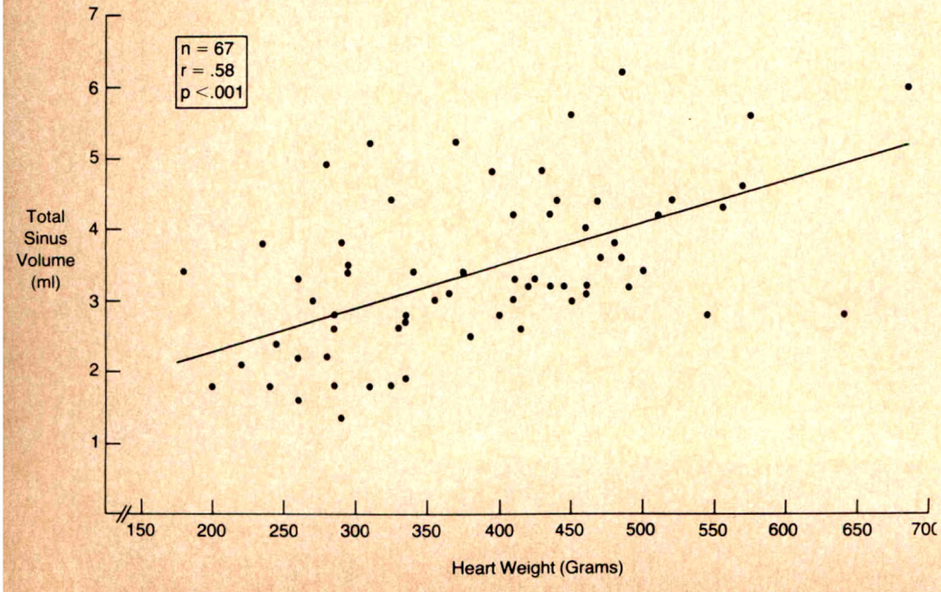

FIGURE 9. Relation of sum of volumes of the 3 sinuses of Valsalva to heart weight.

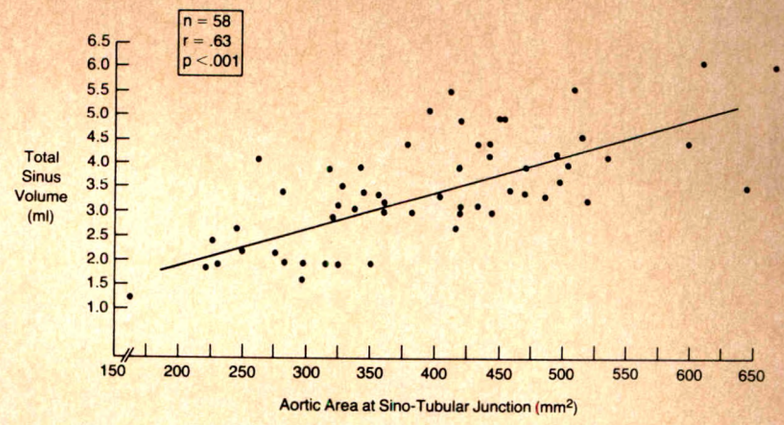

FIGURE 11. Relation of sum of volumes of all 3 sinuses of Valsalva to aortic area at sinotubular junction.

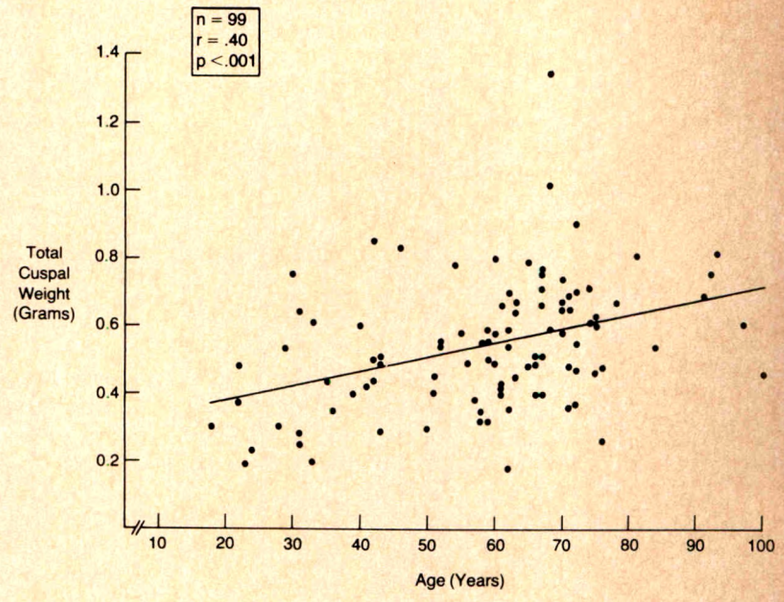

FIGURE 12. Relation of sum of weights of the 3 aortic valve cusps to age.

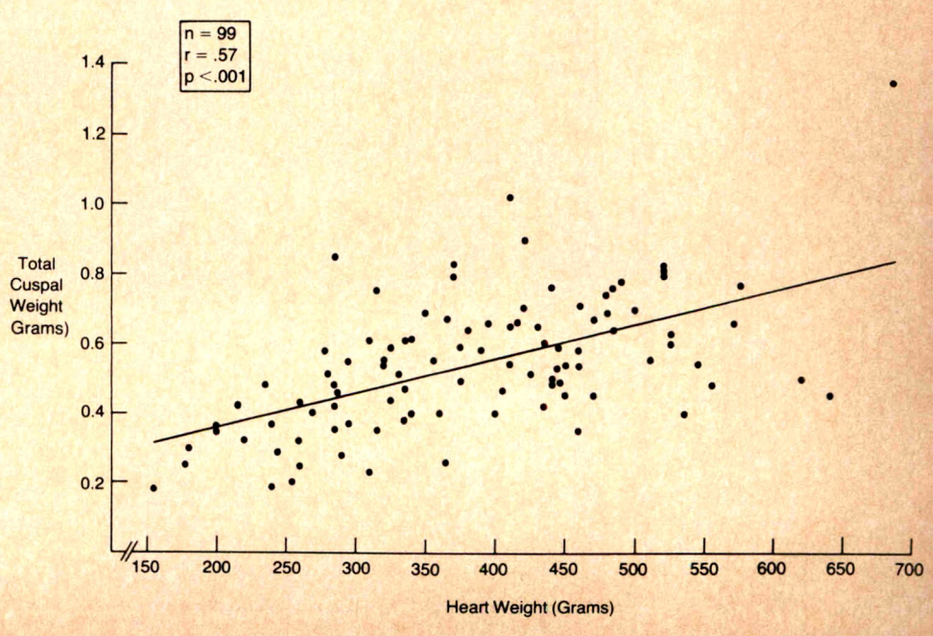

FIGURE 13. Relation of sum of weights of the 3 aortic valve cusps to heart weight.

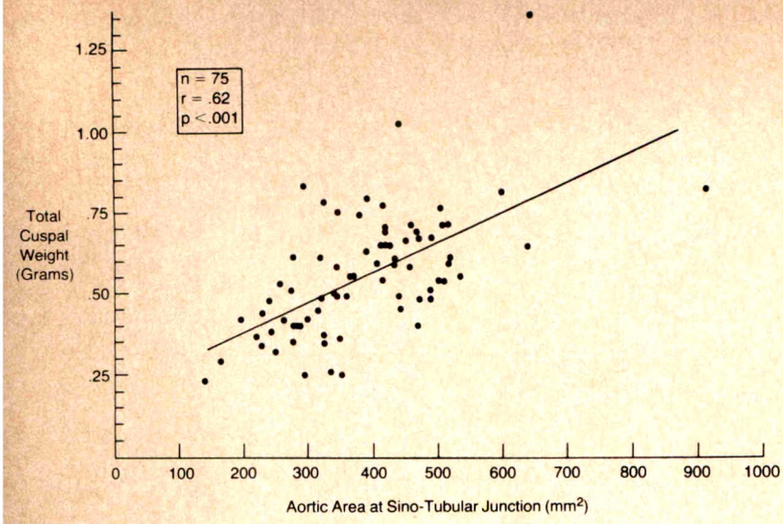

FIGURE 14. Relation of sum of weights of the 3 aortic valve cusps to aortic area at sinotubular junction.

hearts ≤400 g was 139 to 520 mm^2 (mean 333 ± 94); and in the 35 patients with hearts >400 g it was 256 to 915 mm^2 (mean 459 ± 124).

Discussion

The present observations provide detailed data on the area, weight and certain linear measurements on each of the aortic valve cusps and on the volumes of the sinuses of Valsalva in necropsied persons with normally functioning aortic valves. The sums of the aortic valve cuspal areas, cuspal weights and sinus of Valsalva volumes increased with age ($p < 0.001$) and with heart weight ($p < 0.001$). All 3 variables (cuspal area, cuspal weight and sinus of Valsalva volume) also increased with age and heart weight relative to each other. Additionally, the luminal area at the sinotubular junction also increased with age and heart weight, and it also increased as the sum of the aortic valve cuspal areas and weights and sinus of Valsalva volumes increased.

Detailed measurements of the aortic valve cusps disclosed that in only 16% of the patients were the 3 aortic valve cusps of similar sizes (<5% difference in area between cusps); in 51% of patients 1 cusp was of different size from the other 2, and in 33% of patients all 3 cusps were of different sizes. That aortic valve cusps are often of different size was pointed out by Roberts[2] in 1970, but actual measurements on each cusp were not performed. Vollebergh and Becker[3] in 1977 measured the "width," a measurement corresponding to our measurement 4 (Fig. 2), and "height," a mea-

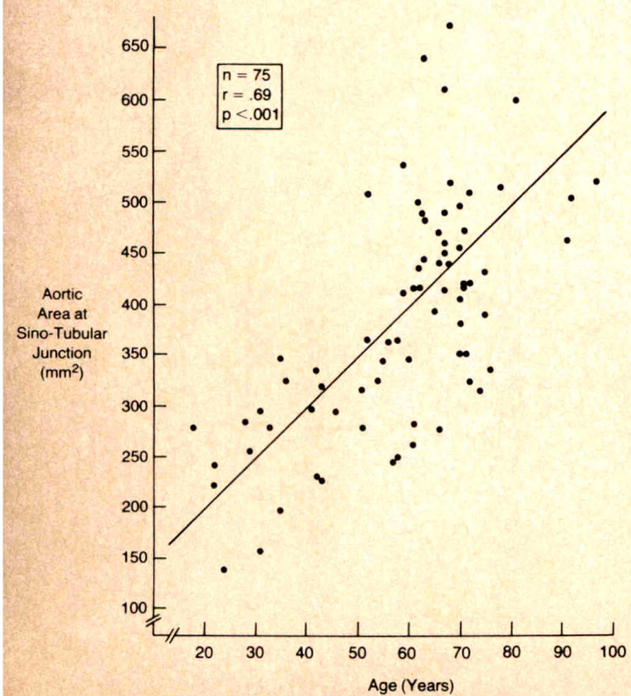

FIGURE 15. Relation of aortic area at sinotubular junction to age.

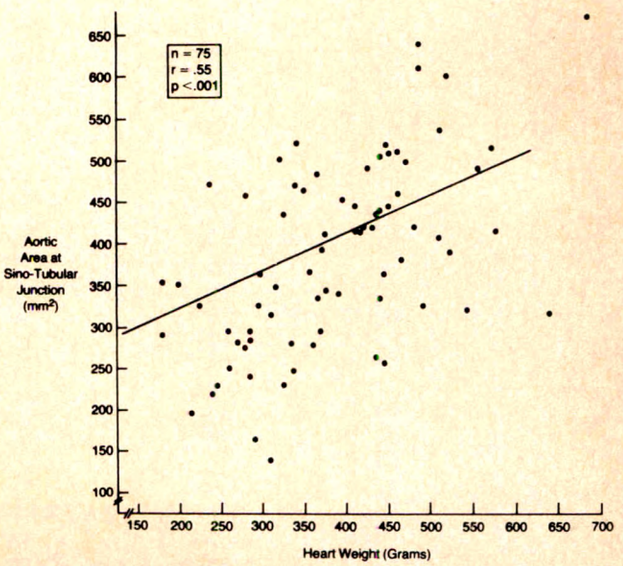

FIGURE 16. Relation of aortic area at sinotubular junction to heart weight.

surement corresponding to our measurement 3 (Fig. 2), in 200 necropsy patients ". . . who had no clinical signs of aortic stenosis and no other cardiac abnormality that could have affected the aortic valve." Both height and width of each cusp were usually different in each patient. The actual heights of the 3 cusps were not provided, however; the results of these measurements were expressed as a percentage of the width of the same cusp. The average width of the right cusp was 25.9 mm; that of the posterior cusp 25.5 mm and that of the left cusp 25.0 mm. Whether or not these differences are significant was not stated. These investigators also calculated the area of each cusp by applying the formula $\pi/4$ (width × height). Using this formula, they found that only 5 of the 200 hearts had cusps of equal areas and that 53 of the 54 hearts of patients younger than 40 years of age had cusps of unequal areas.

In contrast to the few studies describing measurements on the aortic valve in human beings,[3,4] several reports have described results of measurements on the ascending aorta. Krovetz[5] recalculated data gathered initially by Sutter[6] in 1897 and by Kani[7] in 1910 and demonstrated that the size of the aorta, at the level of the sinuses of Valsalva and 1 cm above the sinotubular junction and expressed as cross-sectional area per square meter of body surface area, decreases during the first 20 years of life and increases thereafter (r = 0.77). Several groups of investigators have described results of measuring the circumference of the aorta, presumably at the sinotubular junction, at necropsy. De La Cruz et al,[8] Rowlatt et al,[9] and Eckner et al[10] measured aortic circumference in children and found that it related to body surface area, weight and age. Hutchins and Anaya,[11] Davies[12] and Westaby et al[13] found wide variation in the circumference or diameter of the proximal aorta in adults and it was not importantly related to the size of the patient but it did increase with age.

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Echophonocardiographic Estimates of Pulmonary Artery Wedge Pressure in Mitral Stenosis

PETER S. RAHKO, MD, JAMES A. SHAVER, MD, ROSEMARIE SALERNI, MD, WILLIAM H. GAMBLE, MD, and P.S. REDDY, MD

The efficacy of noninvasive indexes for predicting pulmonary artery wedge (PAW) pressure was reviewed in 77 patients with mitral stenosis. M-mode echocardiography and phonocardiography were used to measure the aortic valve closure–mitral valve E-point interval (A2-E) and the electrocardiographic Q wave–mitral valve closure interval (Q-C) close to the time of diagnostic cardiac catheterization. During catheterization, in 65 patients PAW pressure was measured and in 12 left atrial (LA) pressure was measured. The A2-E and Q-C intervals taken alone had only modest correlation with PAW pressure ($r = -0.54$ and $r = 0.46$, respectively). The correlation was weakest in patients with atrial fibrillation and best in sinus rhythm when heart rate variation between invasive and noninvasive studies was within ±5 beats. Substitution of V-wave pressure for mean PAW pressure and correction for variation in blood pressure improved the A2-E correlation ($r = -0.64$), as did combining the A2-E and Q-C intervals into a ratio [(Q-C)/(A2-E)] ($r = 0.62$). However, the best results were obtained in patients where LA pressure was measured directly ($r = -0.91$ for A2-E), suggesting the PAW pressure is not always an accurate reflection of LA pressure. In conclusion, many factors in addition to LA pressure affect the Q-C and A2-E intervals which, in many situations, decrease their predictive value. However, if used appropriately, these intervals may allow an estimation of PAW pressure.

(Am J Cardiol 1985;55:462–469)

Several echocardiographic[1–4] and phonocardiographic[5–8] indexes have been developed in an attempt to predict noninvasively pulmonary artery wedge (PAW) pressure. The oldest and most widely used method was originally derived in patients with mitral stenosis (MS), in whom both the interval from the electrocardiographic Q wave to mitral valve closure (Q-C) or first heart sound (Q-S1) and the interval from aortic valve closure to peak mitral valve opening (A2-E) or opening snap (A2-OS) are directly related to mean PAW pressure.[5–7] Other investigators later demonstrated that if these intervals were combined as a difference [(Q-C)-(A2-E)] or ratio (Q-C)/(A2-E), the strength of the relation improved.[8–10] These results have been extended from MS to all forms of cardiac disease, and studies using the (Q-C)/A2-E ratio have shown strong correlation with PAW pressure.[10–13] However, several variables in addition to PAW pressure affect the duration of both the Q-C and A2-E intervals, and in some situations, such as mitral regurgitation, the correlation of 1 of the intervals may be lost.[14] Thus, it is doubtful that 1 general equation can accurately predict PAW pressure in all situations. The present study evaluates the hemodynamic determinants of each of these intervals and the resultant ability of these intervals to accurately predict PAW pressure in a homogeneous population of patients with MS.

From the Division of Cardiology, Department of Medicine, University of Pittsburgh School of Medicine, Presbyterian-University Hospital, Pittsburgh, Pennsylvania. Dr. Rahko is supported in part by USPHS Grant HL07557-01. Manuscript received August 28, 1984; revised manuscript received November 1, 1984, accepted November 2, 1984.

Address for reprints: James A. Shaver, MD, Division of Cardiology, University of Pittsburgh, 789 Scaife Hall, Pittsburgh, Pennsylvania 15261.

Methods

Records of patients with MS who were studied between June 1974 and October 1983 were reviewed. Patients with coexistent mitral regurgitation greater than 1+/4+ by left ventricular (LV) angiography, aortic regurgitation greater than 1+/4+ by aortic root angiography or aortic stenosis with mean pressure gradients greater than 20 mm Hg were excluded. The study group consisted of 77 patients (63 women and 14 men) aged 21 to 79 years (mean 49). Thirty-nine patients were in normal sinus rhythm, 37 in atrial fibrillation and 1 in atrial flutter.

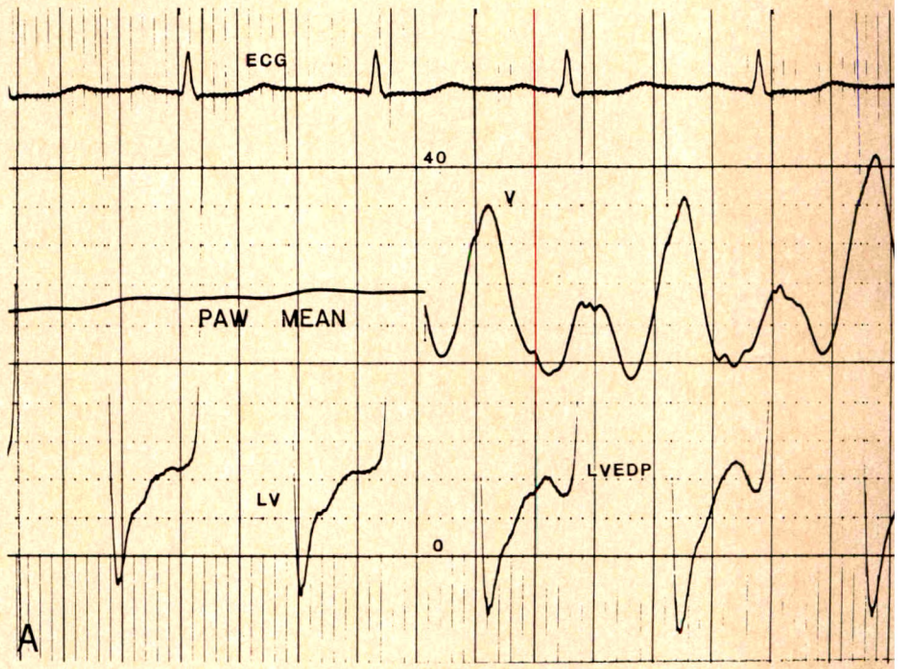
Invasive data: All patients underwent diagnostic right- and left-sided cardiac catheterization and angiography in the fasting state. In 65 patients, the mitral gradient was determined by simultaneous recordings of LV and PAW pressures obtained with either a No. 7Fr Lehman or Swan-Ganz cath-

eter, which was adequately flushed to prevent damping and in stable position confirmed by fluoroscopy. In 12 patients, direct left atrial (LA) pressures were recorded using a Ross transseptal catheter. All recordings were obtained on a multichannel physiologic recorder.

Peak LV systolic, mean PAW or LA, PAW or LA V-wave and LV end-diastolic pressures were determined by averaging the pressures of a complete respiratory cycle. In patients who had simultaneous LA and LV pressures recorded, the pressure at LA–LV crossover in early systole was also obtained (Fig. 1).

Noninvasive data: All patients underwent both M-mode echocardiography and phonocardiography and 67 patients were examined within 4 days of catheterization. Ten patie were studied within 5 to 20 days of catheterization, and significant clinical change was manifested during the inter period.

Patients were studied with simultaneous recordings of t phonocardiogram, mitral valve echocardiogram and electr cardiogram except for 6 patients who had separate recordir of the phonocardiogram and echocardiogram during the sa study. Heart rates were within 2 beats for these 6 patients. recordings were made on a multichannel photographic corder and 66 studies were recorded at a paper speed of 1 mm/s with 20-msec time lines, allowing interval measu ments to within ±4 ms.[15] The 11 remaining studies were



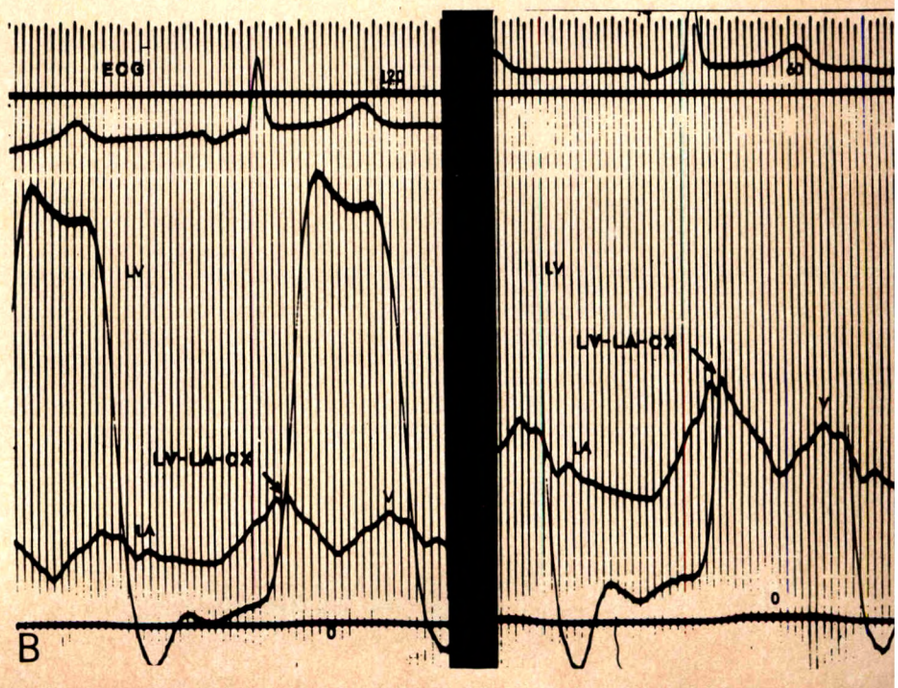


FIGURE 1. A, simultaneous electrocardiogram, left ventricular (LV) pressure and pulmonary artery wedge (PAW) pressure illustrating the pressures measured. Scale is 0 to 40 mm Hg. **B,** simultaneous tracing of the electrocardiogram, LV pressure and left atrial (LA) pressure illustrating pressures measured. The scale is 1 to 120 mm Hg in the **left** panel and 0 to 60 mm Hg in the **right** panel. LA-LV CX = LA–LV pressure crossover point; LVEDP = LV end-diastolic pressure; V = V-wave pressure.

TABLE I Correlation of the Noninvasive Intervals A2-E and Q-C with Various Hemodynamic Pressure Measurements

Test	PAW and LA (n = 77)	PAW Only (n = 65)	LA Only (n = 12)
A2-E vs mean PAW or LA	−0.54	−0.49	−0.91
A2-E vs V-wave	−0.55	−0.52	−0.89
A2-E vs V/LV	−0.64	−0.60	−0.92
Q-C vs mean PAW or LA	0.46	0.49	0.53*
Q-C vs LA-LV crossover	. . .	. . .	0.56*
Q-C vs (LA-LV crossover)—(LV end diastolic)	. . .	. . .	0.62*
(Q-C)/(A2-E) vs mean PAW or LA	0.62	0.60	0.87
[(Q-C)-(A2-E)] vs mean PAW or LA	0.63	0.62	0.85

* $p < 0.038$; in all other cases, $p < 0.00025$. Intervals are as defined in the text.
LA = left atrial pressure; LA-LV crossover = pressure at the early systolic crossover of left ventricular and LA pressure, LV end-diastolic = left ventricular end-diastolic pressure; PAW = pulmonary artery wedge pressure; V-wave = peak of the V-wave pressure; V/LV = peak of the V-wave pressure divided by peak LV pressure.

corded at 50 mm/s with 20-ms time lines. Phonocardiograms were obtained from the second left intercostal space and the cardiac apex using standard microphones. All patients were examined in the supine or in the left lateral position and the mitral valve echocardiogram was obtained using standard techniques. In patients with atrial fibrillation, complexes with R-R intervals as closely as possible approximating the R-R intervals used in recording the pressures at catheterization were chosen.

The following intervals were measured from 5 cardiac cycles and averaged (Fig. 2):

(1) A2-E, A2-OS: The intervals from the first high-frequency vibration of the aortic component of the second heart sound (A2) to the next 2 points: (a) the maximal early diastolic excursion point (E) of the anterior mitral leaflet or (b) the first high frequency vibration of the opening snap (OS).

(2) Q-C, Q-S1: The intervals from the onset of the QRS complex of the electrocardiogram (Q) to either (a) the point of termination of the last posterior motion of the mitral valve anterior leaflet (C)[16] or (b) the first high-frequency component of the first heart sound (S1).

The hemodynamic and noninvasive measurements were made independently. The noninvasive intervals were compared to the invasive measurements of PAW, LA or LA-LV crossover pressure by linear regression analysis.

Results

All study patients had MS, with LA-LV or PAW-LV mean diastolic pressure gradients averaging 13 mm Hg (range 2 to 32). Almost all patients had normal LV function. The average LV end-diastolic pressure was 9 mm Hg (range 1 to 20; greater than 14 mm Hg in only 3 patients) and the average ejection fraction was 58% (range 46 to 82). Peak LV pressure averaged 123 mm Hg (range 90 to 175).

Heart rate averaged 77 beats/min (range 53 to 123). Since the invasive and noninvasive studies were not simultaneous, there was heart rate variation between studies. The correlation, by linear regression, between heart rates in the invasive and noninvasive studies was $r = 0.71$ ($p < 0.00001$). To determine whether or not heart rate variation may have adversely affected the results for the group as a whole, progressively tighter restrictions were placed on the allowable heart rate range with each of the correlations reported in the study. There was no improvement in any correlation as the allowed heart rate variation was decreased. However, the groups formed by applying the heart rate re-

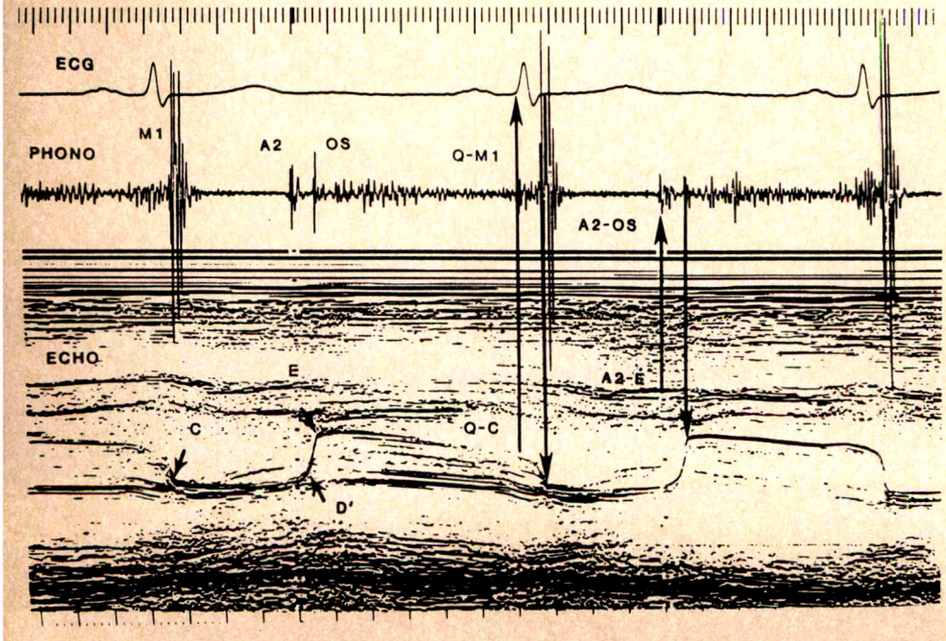


FIGURE 2. Simultaneous electrocardiogram, phonocardiogram and echocardiogram illustrating intervals measured. Intervals are described in the text. A2 = aortic component of second heart sound; C = closure point of mitral valve; D′ = point of first onset of most rapid anterior motion of the mitral valve; E = mitral valve E point; M1 = mitral valve component of the first heart sound; OS = opening snap.

TABLE II Effect on Heart Rate Variation Between Noninvasive and Invasive Studies in Patients in Sinus Rhythm and a Comparison of Correlations Between A2-E and Q-C in Sinus Rhythm and Atrial Fibrillation

	All Patients (n = 77)	Atrial Fibrillation (n = 38)	Sinus Rhythm (n = 39)	Sinus Rhythm + 5 (n = 14)
A2-E vs mean PAW or LA	−0.54	−0.42	−0.63	−0.78
A2-E vs V-wave	−0.55	−0.39	−0.68	−0.83
A2-E vs V/LV	−0.64	−0.52	−0.72	−0.78
Q-C vs mean PAW or LA	0.46	0.44	0.47	0.67
(Q-C)/(A2-E) vs mean PAW or LA	0.62	0.60	0.64	0.83
[(Q-C)-(A2-E)] vs mean PAW or LA	0.63	0.58	0.67	0.84

$p < 0.0008$ for all correlations.
Sinus rhythm ±5 = No greater than a 5-beat variation in heart rate between the invasive and noninvasive studies. All other abbreviations as in Table I.

striction were comprised mainly of patients who were in atrial fibrillation. Thus, the results are analyzed first for the group as a whole and then repeated after division into groups containing only atrial fibrillation and only sinus rhythm.

Both the A2-E and A2-OS intervals were measured. The opening snap was absent in 26% of subjects, but in the remainder the A2-OS interval correlated almost exactly with A2-E (r = 0.99) (Fig. 3A). The Q-S1 and Q-C intervals could be measured in all patients and correlated very well with each other (r = 0.98) (Fig. 3B). In this study, the Q-C and A2-E intervals were used for all pressure correlations.

The average mean PAW pressure was 18 mm Hg (range 5 to 45) and the average V wave of the PAW or LA pressure was 22 mm Hg (range 6 to 52). The mean and V-wave pressures correlated closely with each other (r = 0.84).

There was a significant negative correlation of the A2-E interval with both mean PAW and LA pressures and also with the V wave of PAW and LA pressure. (Table I.) The correlation was much stronger for LA than for PAW pressure. Dividing the V-wave pressure by peak LV pressure to correct for systemic blood pressure variation further strengthened the correlations (Table I).

The Q-C interval significantly correlated with mean PAW and LA pressures, but the correlation was not as great as with the A2-E interval (Table I). With this interval, restricting the analysis to only the LA pressure group resulted in only minor improvement in the correlation. In the LA pressure group, correlation was also made with LA-LV crossover pressure and Q-C, but only minor improvement was noted. A further attempt to correct for variations in LV end-diastolic pressure by comparing Q-C to [(LA-LV crossover pressure) − (LV end-diastolic pressure)] also resulted in minor further improvement in the correlation (Table I).

The combination of the Q-C and A2-E intervals into either a ratio (Q-C/A2-E) or difference [(Q-C)-(A2-E)] was correlated with mean PAW and LA pressures. For the group as a whole and for the PAW pressure group, there was, compared with either interval alone, an improvement in the strength of the correlations (Table I). However, in the LA group, the strength of the correlation decreased compared with the correlation with A2-E alone (Table I).

The above relations were then reanalyzed separately for those with atrial fibrillation and those with sinus rhythm. The correlations were weaker in those with atrial fibrillation and stronger in those with normal sinus rhythm, particularly with the A2-E interval. In the sinus rhythm group, if the heart rate variation between invasive and noninvasive studies was restricted to ±5 beats, all correlations improved further (Table II).

Discussion

Several echocardiographic,[1–4] phonocardiographic[5–9,17–19] and combined echophonocardiographic[10–14] indexes have been developed to noninvasively predict PAW pressure. The most successful has been the ratio

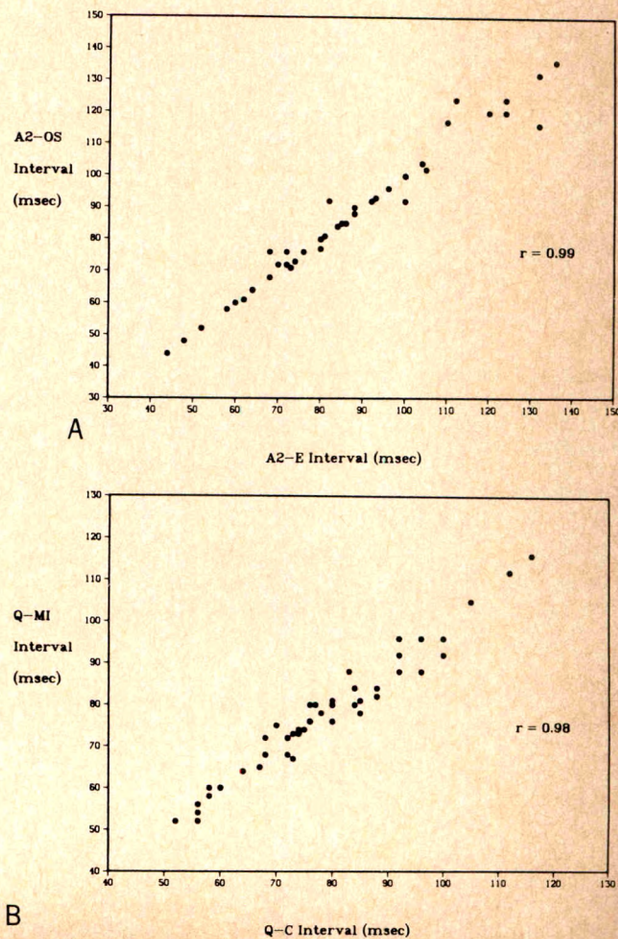


FIGURE 3. A, relation between A2-E interval and the A2-OS interval. **B,** relation between the Q-C interval and the Q-M1 interval.

of (Q-C)/(A2-E) for which several predictive regression equations have been published.[9–13]

The A2-E interval defines a period of time in early diastole during which pressure in the LV rapidly falls from the time of aortic valve closure to the point of maximal anterior deflection of the mitral valve leaflets (Fig. 4). The fundamental assumption which makes this interval useful is that as LA pressure rises, the time from A2 to pressure crossover shortens and hence the A2-E interval shortens.

However, several other variables besides LA pressure help determine the A2-E interval, thus decreasing the consistency of the relation between patients with different types of cardiac disease. LV pressure at the time of A2 may vary considerably. Thus, for a given LA pressure, a hypertensive patient will have a larger pressure drop and, hence, a longer A2-E interval than a hypotensive patient. Since LV pressure at the time of A2 is difficult to measure, peak LV pressure has been used instead and V/LV or the difference LV-V has been used to correct for variation in LV pressure at the time of aortic closure. As demonstrated in this study and previously,[8,9] this generally results in an improved correlation with A2-E (Fig. 5).

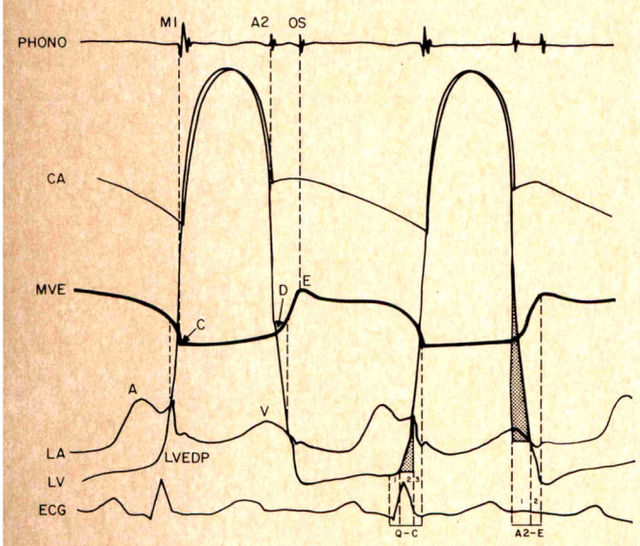


FIGURE 4. Simultaneous micromanometer-derived left ventricular (LV), left atrial (LA) and central aortic pressures with an electrocardiogram, phonocardiogram and mitral valve echocardiogram (MVE) to illustrate the interrelationships between sound, mitral valve motion and hemodynamic events that affect the A2-E and Q-C intervals. The **left** complex shows that pressure crossover occurs before mitral valve closure and the C point, or closure point, of the mitral valve is coincident with the mitral component (M1) of the first heart sound. LV pressure at the time of A2 is demonstrated and the mitral valve E point and opening snap are coincident. Mitral valve opening (D point) begins before pressure crossover. In the **right** complex, the determinants of the 2 intervals are shown. The Q-C interval may be divided into 3 sections. Section 1 represents electromechanical coupling of the left ventricle from the Q wave to the onset of pressure increase. Section 2 represents the time needed to overcome the difference between LA pressure and LV end-diastolic pressure (LVEDP) and will prolong as the pressure gap between the 2 chambers widens. Section 3 represents the interval from pressure crossover to actual mitral valve closure and is a function of mitral valve compliance and momentum of the forward-flowing blood column. The A2-E interval may be divided into 2 sections. Section 1 represents the time from A2 to pressure crossover and will be affected by the rate of LV pressure decrease (−dP/dt), the LV pressure at the time of A2 and LA pressure at the time of pressure crossover. Section 2 is a function of the compliance of the mitral valve. A = A wave of left atrial pressure; CA = central aortic pressure, D = onset of opening of the mitral valve; phono = phonocardiogram; other abbreviations as defined in Figures 1 and 2.

By relating A2-E to the V-wave pressure instead of mean LA or PAW pressure, there should theoretically be an improvement in correlation, since the V wave occurs during the A2-E interval and determines the point where the mitral valve begins to open (Fig. 4). The importance of using the V wave becomes proportionately greater as the degree of mitral regurgitation increases. When significant regurgitation is present, the A2-E interval taken alone correlates more strongly with PAW pressure than the ratio Q-C/A2-E.[10] In the present study, significant mitral regurgitation was purposely excluded and, thus, there was only a slight improvement in the A2-E relation when V-wave pressure was substituted for mean LA or PAW pressure. (Table I).

The mobility of the mitral valve probably plays only a minor role in the A2-E interval. Mitral valve motion is initiated slightly before LA-LV pressure crossover and the E point clearly occurs after crossover[20,21] (Fig. 4). However, the exact timing of the E point relative to pressure crossover is variable and is not directly related to either the severity of MS or the height of LA pressure.[20,21]

The rate at which LV pressure decreases because of relaxation is the other major independent factor affecting the A2-E interval. Since relaxation rate may vary, depending on the presence of certain primary myocardial diseases, the consistency of the A2-E relation between patients with different myocardial disease states but the same PAW pressure will be decreased. In this study, variation in relaxation rate, except that related to differences in peak LV pressure,[22] should have been minimal since LV function was essentially normal in all.

The Q-C interval is a measure of the initial events of systole and multiple factors affect its length.[14] In patients with MS, if all other variables are held constant, the interval should lengthen as LA pressure increases due to an increasing pressure difference between LV end-diastolic pressure and LA pressure (Fig. 4). This study has shown the Q-C correlation with mean LA or PAW pressure to be weaker than the corresponding A2-E correlation. Even when LA-LV crossover pressure is precisely defined, there is little further improvement in correlation (Table I).

In MS, the relation of mitral valve closure to LA-LV pressure crossover is analogous to the relation previously discussed with opening in that the C point does not occur until after pressure crossover[20,21] (Fig. 4). Again, there is a range of variation in the LA-LV pressure crossover to C-point interval, but there is no clear relation to LA pressure, mitral mobility or other factors.[20,21] When significant mitral regurgitation is present, the correlation between Q-C and mean PAW or LA pressure disappears.[14] This may reflect the fact that the large V-wave pressure, which has no physiologic relationship to Q-C, is the primary determinant of LA

or PAW pressure when mitral regurgitation is present.

Several studies using the (Q-C)/(A2-E) ratio in patients with normal mitral valves have demonstrated significant relationships between the Q-C interval and either PAW or LV end-diastolic pressure.[10–13] Because in these patients a pressure difference between LV end-diastolic and LA pressure is no longer present, the Q-C interval does not represent the time delay for LV pressure to exceed LA pressure. Instead, it probably represents a progressive decrease in positive dP/dt that occurs when LV dysfunction is present.[23] Other factors that affect the Q-C interval include the length of the PR interval and the presence of conduction system disease affecting the left ventricle.[24]

Since the Q-C and A2-E intervals change in opposite directions as LA pressure increases, the combination of these intervals into a difference [(Q-C)-(A2-E)] or ratio (Q-C)/(A2-E) has been used to accentuate the effect of pressure changes and minimize the effect of the other variables.[8–13] Our study agrees with others in that the combinations of the 2 intervals have a stronger correlation with PAW pressure than either interval taken alone (Fig. 6). However, in the subgroup of patients who underwent transseptal catheterization, there was marked improvement in the A2-E interval correlations but little improvement in the Q-C relation. Thus, when the 2 intervals are combined, the correlation with mean LA pressure decreases, probably because the weaker Q-C relation detracts from the stronger A2-E relation. It is generally assumed that mean PAW pressure is an accurate reflection of mean LA pressure; thus, it is somewhat surprising in this study that there was also a marked improvement in mean LA pressure correlation with A2-E compared with mean PAW pressure. The reason for enhanced correlation with LA as opposed to PAW pressure is probably the effects of damping, which occur to some degree in all PAW pressure tracings. This

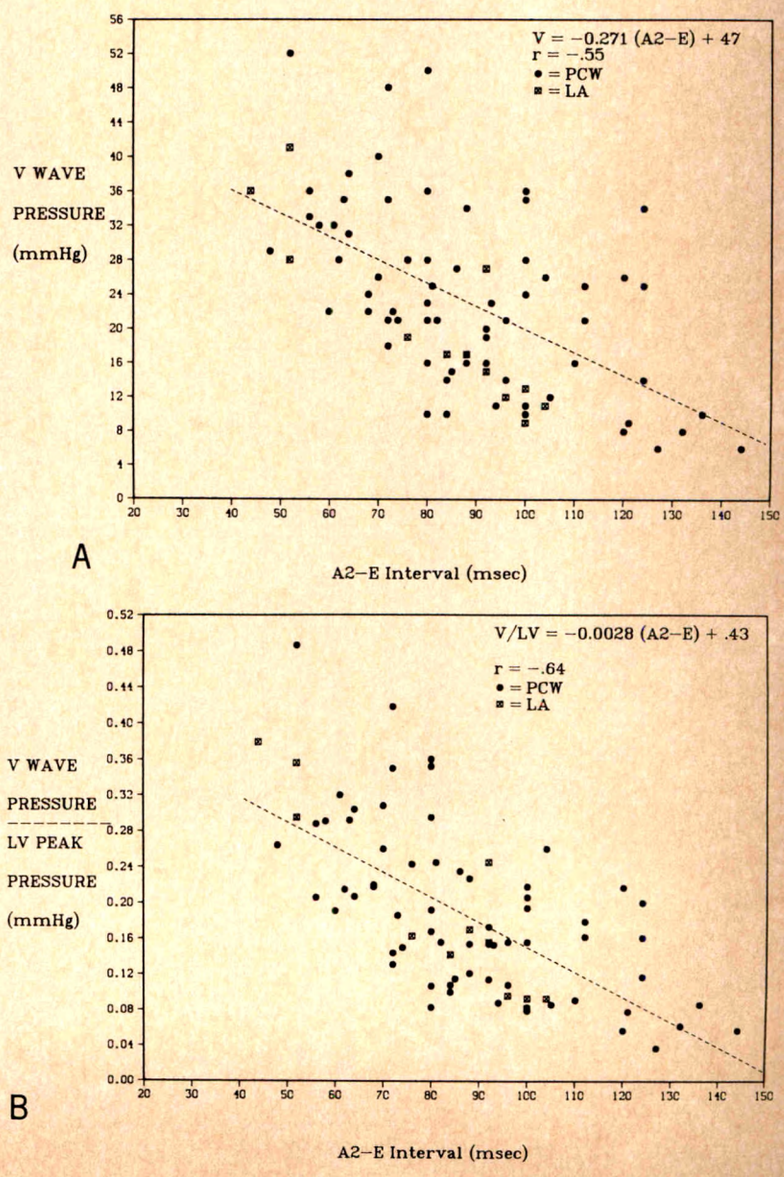


FIGURE 5. A, relation between the A2-E interval and V-wave pressure of both the pulmonary artery wedge (PAW) and left atrial (LA) pressures. **B,** relation between the A2-E interval and (V-wave pressure)/(peak left ventricular pressure) illustrating the improvement in correlation noted when correction is made for variation in peak left ventricular pressure.

TABLE III Comparison of Predicted Pulmonary Artery Wedge Pressure from Five Linear Regression Equations When a Spectrum of Values for (Q-C)/(A2-E) Is Substituted

Study	Regression Equation	r Value	Predicted PAW Pressure When the Ratio of (Q-C)/(A2-E) is: 0.25	0.5	0.75	1.0	1.5	2.0
Yigitbasi et al[9]*	17.8x + 1.33	0.91	6	10	15	19	28	37
Palomo et al[10]†	21.6x + 1.1	0.93	6	12	17	23	33	44
Abdulla et al[11]‡	18.8x + 1	0.87	6	11	16	21	30	39
Askenazi et al[13]§	34.2x − 2.1	0.91	6	15	24	32	49	66
Present study	12.8x + 6.0	0.62	9	12	16	19	25	32

* Phonocardiographic study in mitral stenosis using (Q-S1)/(A2-OS); † used (Q-C)/(A2-E) vs left ventricular end-diastolic pressure, but also used to predict pulmonary artery wedge pressure with and without mitral stenosis; ‡ used (Q-C)/(A2-E) vs pulmonary artery wedge pressure in patients without mitral stenosis; § did not use phonocardiogram but used echocardiogram of aortic valve to determine time of A2 in patients without mitral stenosis.

x = (Q-C)/(A2-E) or equivalent.

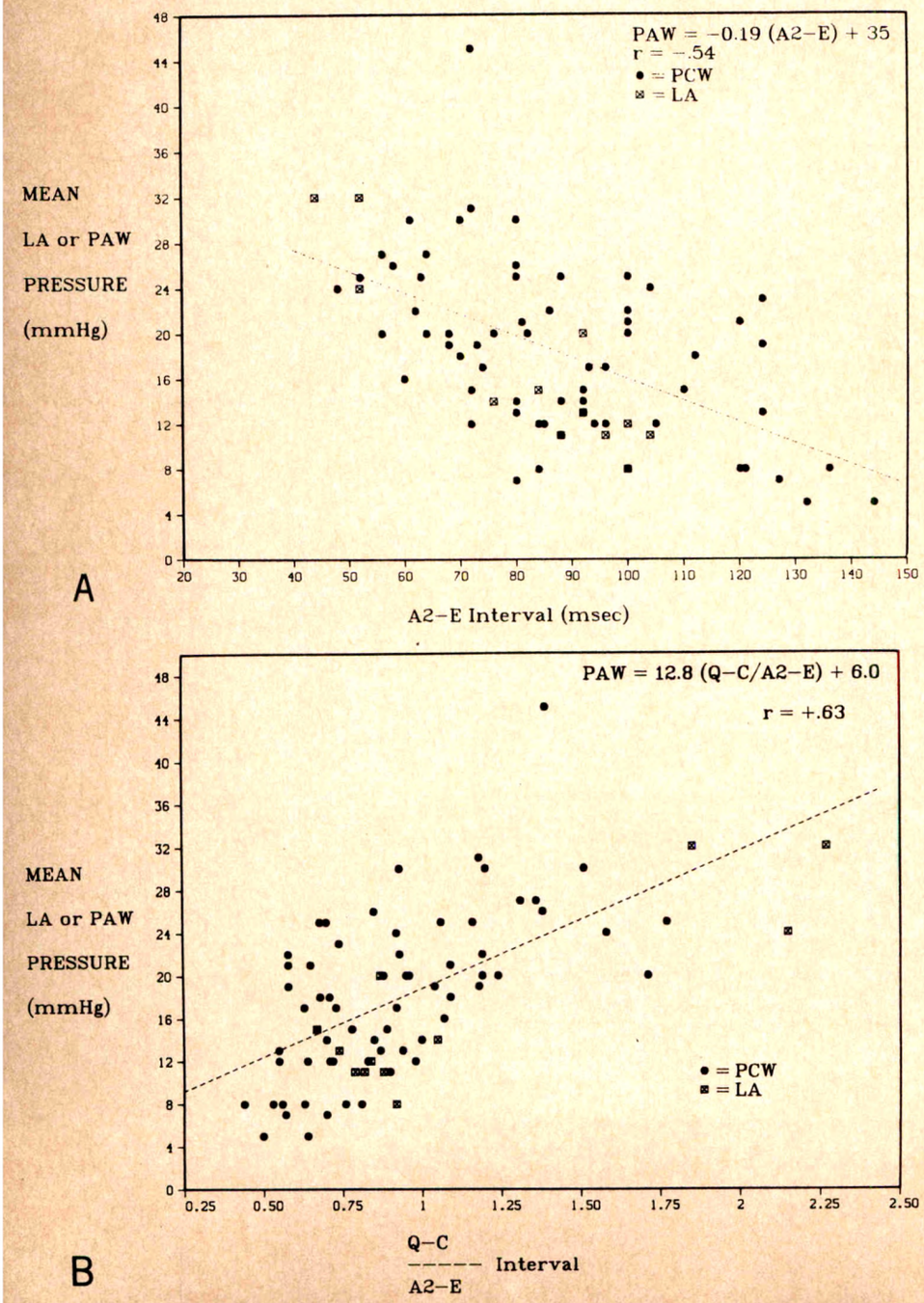


FIGURE 6. A, relation between the A2-E interval and mean pulmonary artery wedge (PAW) and left atrial (LA) pressures. **B,** relation between the ratio of (Q-C)/(A2-E) and mean PAW and LA pressure.

is most likely because of (1) the softer and smaller-lumen catheters used in right-sided cardiac catheterization, particularly balloon-tipped catheters; (2) changes in PAW pressure produced by local variations in pulmonary artery vasculature; (3) variable loss of amplitude of LA pressure variations across the pulmonary capillary bed especially at lower LA pressures; (4) the effects of primary pulmonary disease states; and (5) misinterpretation of a damped pulmonary artery pressure as PAW pressures.[25,26]

Several regression equations to predict PAW pressure have been developed and are listed in Table III, along with the PAW pressure estimates which would be obtained if representative values for the (Q-C)/(A2-E) ratio were substituted to represent a typical spectrum of ratios. Although there is reasonable agreement at low pressures, there is a marked divergence in predicted PAW pressure at high pressures. The variations in these results reflect to some degree minor differences in methodology of data acquisition and measurement. More important, these equations represent the patient population used to generate them and show that it is doubtful, no matter how strong the correlation in a given study is, that 1 regression equation can successfully predict PAW pressure in all patients, because several factors in addition to PAW pressure affect these intervals.

The Q-C and A2-E intervals may be useful for predicting PAW pressure in certain situations if the above limitations are recognized. For example, if a predictive equation is developed in a homogeneous population, that equation should give a reasonable quantitative estimate of PAW pressure in patients with a similar disease. Also, although in most situations the Q-C/A2-E ratio is the best estimation of PAW pressure, in some settings, particularly when significant mitral regurgitation is present or a left-sided conduction delay is noted, the A2-E interval alone is more reliable.

Acknowledgment: We express our appreciation to Alfred Cecchetti for assistance in preparing the statistics and illustrations, to Darlene Yourick for typing the manuscript and to Albert Durica for his assistance with illustrations.

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Medically Directed At-Home Rehabilitation Soon After Clinically Uncomplicated Acute Myocardial Infarction: A New Model for Patient Care*

The University of Alabama School of Medicine designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. Answers are to be marked on the instruction sheet on page 504.

1. In this study, 5 patients were excluded after randomization because of complications after:
   a) elevation of serum creatine kinase
   b) elevation of oxaloacetic transaminase
   c) treadmill exercise testing
   d) new Q waves appeared

2. The mean age of 198 training study participants was:
   a) 64 years
   b) 31 years
   c) 37 years
   d) 52 years

3. Eighty-six percent of the subjects were employed with professional and managerial roles constituting:
   a) 24%
   b) 15%
   c) 56%
   d) 31%

4. Treadmill exercise testing was terminated if the patient experienced:
   a) chest pain, dyspnea, fatigue or leg cramps
   b) hypotension
   c) ventricular tachycardia
   d) any of the above

5. Patients assigned to home training who were free of treadmill angina at 3 weeks were:
   a) in the vast majority
   b) in the minority
   c) instructed to walk briskly
   d) loaned a stationary bike for exercise

6. The program nurse was able to obtain electrocardiographic data on the exercising patient at home by:
   a) telephone and transmission of M-CL5 bipolar lead electrocardiogram
   b) having the patient come in twice weekly
   c) having the patient come in once weekly
   d) having the patient phone in his readings daily

7. Telephone calls permitted verification and detection of changes in:
   a) training intensity
   b) patients clinical status
   c) medication use
   d) all of the above

8. Treadmill-induced ventricular tachycardia in patients who demonstrated treadmill-induced ventricular bigeminy at 3 weeks was absent in:
   a) 52%
   b) 32%
   c) 28%
   d) 14%

9. The number of patients withdrawn from this study solely because of exercise-induced ischemic ST-segment depression was:
   a) 0
   b) 20
   c) 14
   d) 5

10. Of the 600,000 Americans surviving acute myocardial infarction each year, this study suggests that the approximate number capable of safely completing 3 months of at-home rehabilitation is:
    a) 75,000
    b) 300,000
    c) 100,000
    d) none of the above

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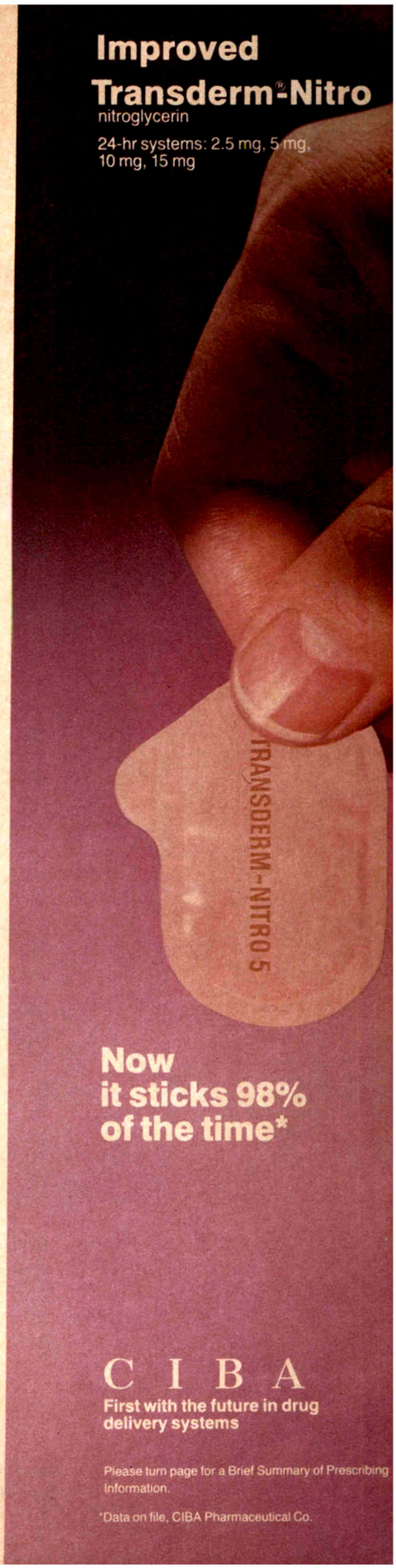

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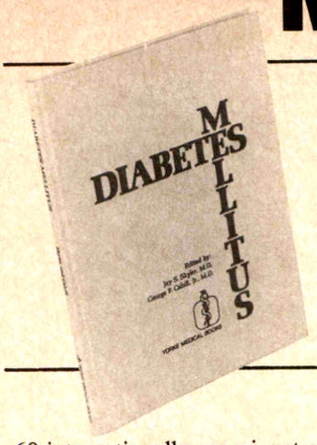

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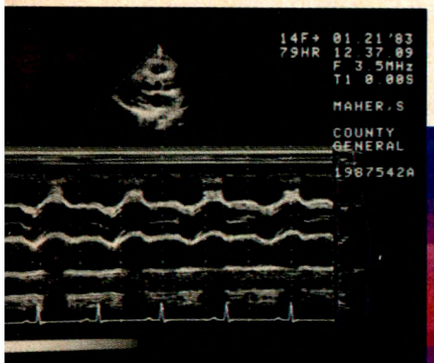

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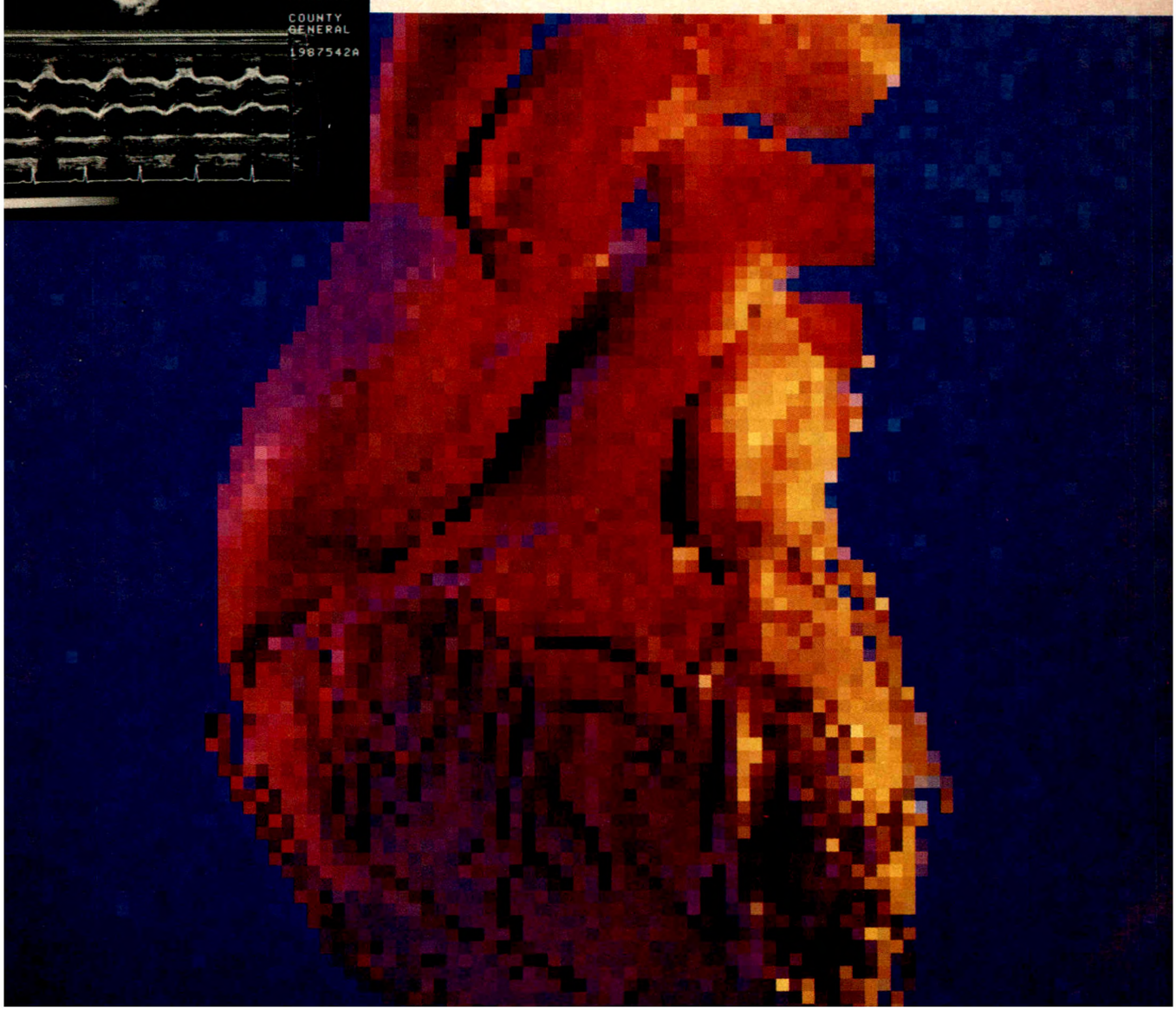

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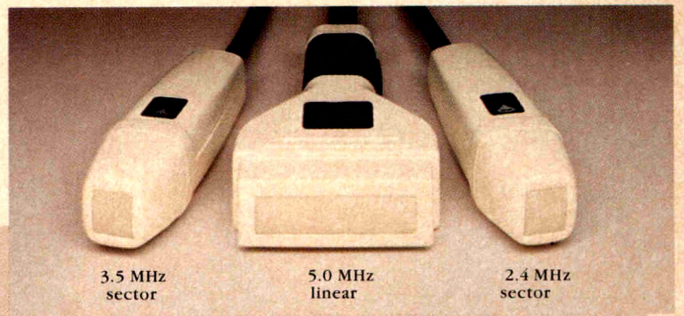

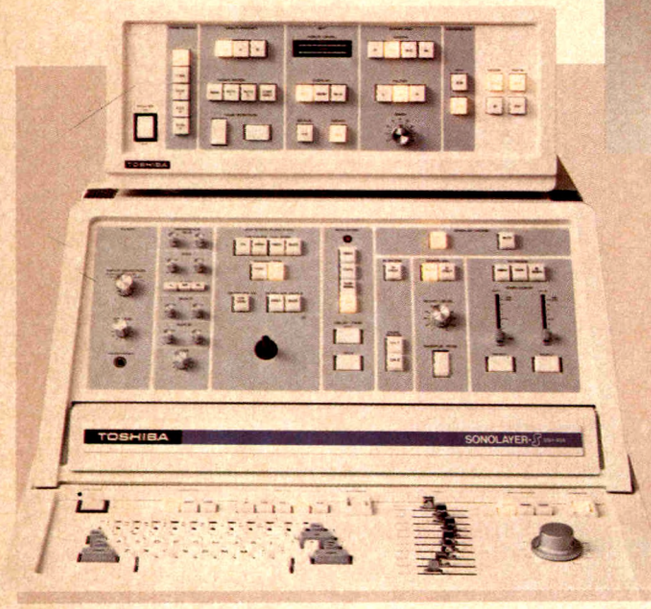

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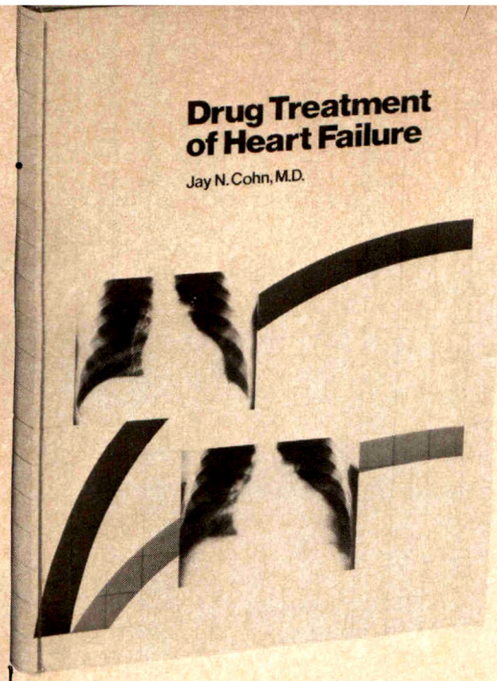

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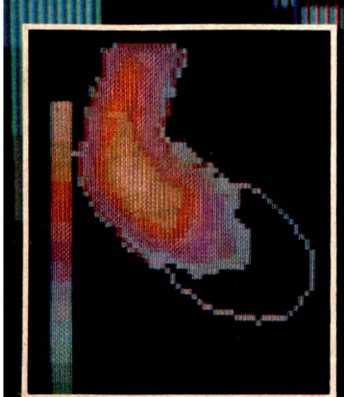

First-pass Radionuclide Angiocardiography displaying a markedly reduced left ventricular ejection fraction in a patient with congestive heart failure. The comparison view (inset at left) shows normal contraction in a patient without heart disease.

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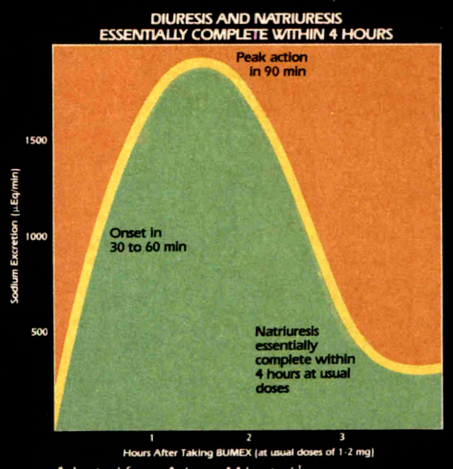
iuresis essentially complete within hours with Bumex at usual doses[1,2]

aster completion of diuresis with unsurpassed ficacy: that's what makes Bumex easy to live ith compared to other loop diuretics.

Bumex rapidly mobilizes a high volume of uid and sodium in edematous patients with ongestive heart failure.[3] And Bumex is unsur-assed in reducing edema and improving the nctional status of CHF patients.[4,5]

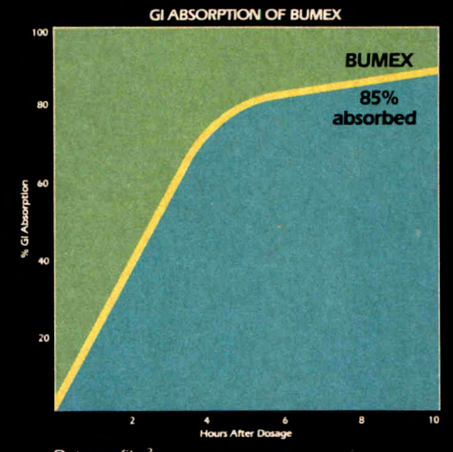


Adapted from Asbury MJ, *et al.*[1]

ffective diuresis through rapid, early complete absorption

ghty-five percent of an oral dose of Bumex absorbed through the GI tract;[3] thus the uretic response you can expect with oral umex is almost equal in magnitude to the sponse you get with an I.V. dose.[3,6]

As with all loop diuretics, excessive doses Bumex can lead to profound diuresis with ater and electrolyte depletion, including ypokalemia. Serum electrolytes should be onitored periodically, especially in patients n low-salt diets or those treated for pro-nged periods or on high doses.



Data on file.[3]

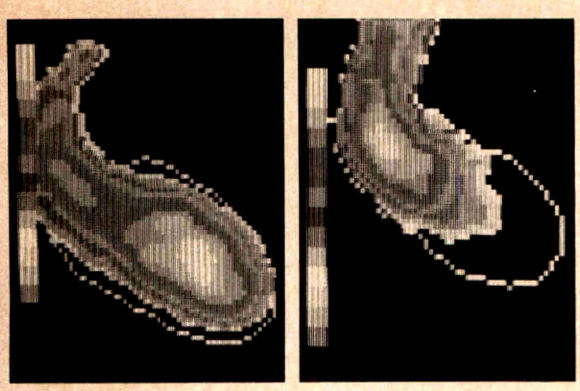
Bumex®

bumetanide/Roche

0.5-mg and 1-mg scored tablets/2-ml ampuls, 2-ml, 4-ml and 10-ml vials (0.25 mg/ml)

Faster completion of diuresis that's easier to live with

Faster completion of diuresis... that's easier to live with.



First-pass Radionuclide Angiocardiography displaying a markedly reduced left ventricular ejection fraction in a patient with congestive heart failure. The comparison view (on right) shows normal contraction in a patient without heart disease.

- Essentially completes diuresis within 4 hours, at usual doses
- Among loop diuretics, unsurpassed in volume of fluid and sodium excreted
- Unsurpassed in reducing edema and improving functional status
- Rapidly, nearly completely absorbed—for a predictable diuretic response
- Allows for early-evening diuresis—for days of normal activity, nights of uninterrupted sleep
- Contraindicated in anuria, markedly elevated BUN, hepatic coma and severe electrolyte deficiency
- The most frequent clinical adverse reactions considered probably or possibly related to Bumex are: muscle cramps, dizziness, hypotension, headache, nausea and encephalopathy.

References: 1. Asbury MJ, *et al: Br Med J 1:* 211-213, Jan 22, 1972. **2.** Davies DL, *et al: Clin Pharmacol Ther 15:*141-155, Feb 1974. **3.** Data on file, Hoffmann-La Roche Inc., Nutley, N.J. **4.** Dixon DW, Barwolf-Gohlke C, Gunnar RM: *J Clin Pharmacol 21:*680-687, Nov-Dec 1981. **5.** Halstenson CE, Matzke GR: *Drug Intell Clin Pharm 17:*786-797, Nov 1983. **6.** Pentikäinen PJ, *et al: Br J Clin Pharmacol 4:*39-44, Jan 1977.

Bumex®

bumetanide/Roche

0.5-mg and 1-mg scored tablets/
2-ml ampuls, 2-ml, 4-ml and 10-ml vials (0.25 mg/ml)
Before prescribing, please consult complete product information, a summary of which follows:

WARNING: Bumex (bumetanide/Roche) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs. (See under DOSAGE AND ADMINISTRATION in complete product information.)

INDICATIONS AND USAGE: Edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.
Almost equal diuretic response occurs after oral and parenteral administration of Bumex. If impaired gastrointestinal absorption is suspected or oral administration is not practical, Bumex should be given by the intramuscular or intravenous route.
Successful treatment with Bumex following instances of allergic reactions to furosemide suggests a lack of cross-sensitivity.
CONTRAINDICATIONS: Anuria. Hypersensitivity and in patients in hepatic coma or in states of severe electrolyte depletion. Although Bumex can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment.
WARNINGS: Dose should be adjusted to patient's needs. Excessive doses or too frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.
Prevention of hypokalemia requires particular attention in patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia is thought to represent particular added risks to the patients.
In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma. Treatment in such patients is best initiated in the hospital with small doses and careful monitoring of the patient's clinical status and electrolyte balance. Supplemental potassium and/or spironolactone may prevent hypokalemia and metabolic alkalosis in these patients.
In cats, dogs and guinea pigs, Bumex has been shown to produce ototoxicity. Since Bumex is about 40 to 60 times as potent as furosemide, it is anticipated that blood levels necessary to produce ototoxicity will rarely be achieved. The potential for ototoxicity increases with intravenous therapy, especially at high doses.
Patients allergic to sulfonamides may show hypersensitivity to Bumex.
PRECAUTIONS: Measure serum potassium periodically and add potassium supplements or potassium-sparing diuretics, if necessary. Periodic determinations of other electrolytes are advised in patients treated with high doses or for prolonged periods, particularly in those on low salt diets.
Hyperuricemia may occur. Reversible elevations of the BUN and creatinine may occur, especially with dehydration and in patients with renal insufficiency.
Bumex (bumetanide/Roche) may increase urinary calcium excretion.
Possibility of effect on glucose metabolism exists. Periodic determinations of blood sugar should be done, particularly in patients with diabetes or suspected latent diabetes.
Patients should be observed regularly for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions.
Especially in presence of impaired renal function, use of parenterally administered Bumex should be avoided in patients to whom aminoglycoside antibiotics are also being given, except in life-threatening conditions.
Drugs with nephrotoxic potential and bumetanide should not be administered simultaneously.
Since lithium reduces renal clearance and adds a high risk of lithium toxicity, it should not be given with diuretics.
Probenecid should not be administered concurrently with Bumex (bumetanide/Roche).
Concurrent therapy with indomethacin not recommended.
Bumex may potentiate the effects of antihypertensive drugs, necessitating reduction in dosage.
Interaction studies in humans have shown no effect on digoxin blood levels.
Interaction studies in humans have shown Bumex to have no effect on warfarin metabolism or on plasma prothrombin activity.
Pregnancy: Bumex should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.
Bumetanide may be excreted in breast milk.
Pediatric Use: Safety and effectiveness below age 18 not established.
ADVERSE REACTIONS: Muscle cramps, dizziness, hypotension, headache and nausea, and encephalopathy (in patients with preexisting liver disease).
Less frequent clinical adverse reactions are weakness, impaired hearing, rash, pruritus, hives, electrocardiogram changes, abdominal pain, arthritic pain, musculoskeletal pain and vomiting.
Other clinical adverse reactions are vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhea, premature ejaculation and difficulty maintaining an erection.
Laboratory abnormalities reported are hyperuricemia, azotemia, hyperglycemia, increased serum creatinine, hypochloremia, hypokalemia, hyponatremia, and variations in CO_2 content, bicarbonate, phosphorus and calcium. Although manifestations of the pharmacologic action of Bumex (bumetanide/Roche), these conditions may become more pronounced by intensive therapy.
Diuresis induced by Bumex may also rarely be accompanied by changes in LDH, total serum bilirubin, serum proteins, SGOT, SGPT, alkaline phosphatase, cholesterol, creatinine clearance, deviations in hemoglobin, prothrombin time, hematocrit, platelet counts and differential counts. Increases in urinary glucose and urinary protein have also been seen.
HOW SUPPLIED: *Tablets,* 0.5 mg (light green) and 1 mg (yellow), bottles of 100 and 500; Prescription Paks of 30; Tel-E-Dose® cartons of 100. Imprint on tablets: 0.5 mg—ROCHE BUMEX 0.5; 1 mg—ROCHE BUMEX 1.
Ampuls, 2 ml, 0.25 mg/ml, boxes of ten.
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A Randomized Trial of Low-Dose Beta-Blockade Therapy for Idiopathic Dilated Cardiomyopathy

JEFFREY L. ANDERSON, MD, JOAN R. LUTZ, RN, EDWARD M. GILBERT, MD, SHERMAN G. SORENSEN, MD, FRANK G. YANOWITZ, MD, RONALD L. MENLOVE, PhD, and MARIAN BARTHOLOMEW

Beta-blockade therapy to improve survival in idiopathic dilated cardiomyopathy (IDC) has been both advocated and criticized. However, randomized studies have not been performed. Thus, 50 patients with IDC were randomized in pairs to standard therapy (C) alone or with β blockade (BB). Beta-blockade therapy with metoprolol was titrated from 12.5 to 50 mg twice daily as tolerated (final average dose, 61 mg/day). Groups were comparable in age (C, 50 ± 15 years; BB, 51 ± 13 years), gender (C, 76% male; BB, 56% male), entry functional class (C, 2.8 ± 0.8; BB, 2.7 ± 0.7), and left ventricular ejection fraction (C, 27 ± 12%; BB, 29 ± 10%). Follow-up averaged 19 months (range 1 to 38). One subject in each group was lost to follow-up. There were 3 early BB dropouts (within 2 days) due to low-output syndrome (2 patients) or fatigue (1 patient). Eleven patients died. By intention to treat, 5 BB and 6 C patients died (difference not significant). By actual treatment, 3 BB patients died, including 2 late dropouts (at 0.2, 10 and 17 months), and 8 C patients died (at 2, 9, 9, 15, 18, 24, 29 and 32 months, p = 0.12). In addition, functional evaluation on follow-up (functional class, San Diego questionnaire and exercise time) all tended to favor those receiving BB. Low-dose BB is tolerated in 80% of IDC patients on a long-term basis. Those continuing to take BB have a good prognosis. Mortality in C patients, however, is less than in some retrospective studies. The improved survival trend in the BB group may be due to selection of less ill patients and to possible protective effects of BB. A randomized multicenter study appears appropriate for definitive evaluation of survival effects of BB in IDC.

(Am J Cardiol 1985;55:471–475)

The use of β-adrenoceptor blocking agents in patients with idiopathic dilated cardiomyopathy (IDC) has been both criticized and advocated. Traditionally, β-blocking drugs have been contraindicated in this condition because of their negative inotropic effects. However, largely uncontrolled trials by the Swedish group suggest low-dose β blockade to be tolerated and beneficial.[1–4] The disease appeared to stabilize, the symptoms lessened, and mortality decreased. In contrast, others have reported negative results.[5,6] Given the poor prognosis despite therapy, the testing of new and unconventional therapies appears appropriate in IDC. We therefore performed a randomized pilot study to investigate the effects of low-dose β blockade on mortality and functional class in patients with IDC.

From the University of Utah School of Medicine and the LDS Hospital, Department of Internal Medicine, Division of Cardiology, Salt Lake City, Utah. Manuscript received August 20, 1984; revised manuscript received October 25, 1984, accepted October 29, 1984.

Address for reprints: Jeffrey L. Anderson, MD, Division of Cardiology, c/o LDS Hospital, 325 8th Avenue, Salt Lake City, Utah 84143.

Methods

Hypothesis: Survival represented the primary hypothesis being tested. Using the statistics from the historically controlled study of Swedberg et al,[2] it was estimated that mortality might approach 50% in the control group at a mean of 1 to 1½ years, compared with 15% in the treated group. A total of 50 patients (25 in each group) was therefore considered adequate to demonstrate significance between the 2 groups at the $p < 0.05$ level. Functional classification represented a secondary variable on which to test the effects of therapy.

Entry criteria: Fifty consecutive adult patients evaluated at our institution with a diagnosis of IDC were recruited under an approved protocol. Patients with overt congestive heart failure were not entered until medically stabilized. IDC was confirmed by its typical echocardiographic pattern of diffuse hypokinesia together with a depressed ejection fraction (less than 40% by radionuclide ventriculography). All patients older than 30 years underwent coronary arteriography to exclude

TABLE I Entry Characteristics by Group

Variable	Control	Beta Blockade
n	25	25
Age (yr)*	50 ± 15	51 ± 13
Gender (% male)	76	56
Functional class*	2.8 ± 0.8	2.7 ± 0.7
LV ejection fraction (%)*	27 ± 12	29 ± 10
Norepinephrine (pg/ml)†	673 ± 347 (18)	547 ± 269 (14)
Average time in study (mo) (entry to June 1984)	23 ± 9	23 ± 9

* Values are expressed as mean ± standard deviation; no differences between groups are significant.
† Testing incomplete; numbers of patients given in parentheses; normal range, 65 to 320 pg/ml.
LV = left ventricular.

TABLE II Individual Death Summary (by Actual Treatment Method)

Pt. No.* & Group	Time (mo)	FC	Cause	Comment
		Beta-Blockade Group		
10BB	0.2	IV	CHF	Concomitant diltiazem
16BB	11	IV	CHF	Stopped BB 2 mo before
9BB	16	III	SD	Stopped BB 3 wk before
		Control Group		
11C	2	III	SD(VF)	Holter documented
9C	9	IV	CHF	Transplanted †
13C	9	IV	SD	Witnessed
7BB	15	IV	?SD	Intolerant of BB (2 doses)
15BB	15	IV	CHF	Intolerant of BB (1 dose)
7C	24	III	SD	During sleep
6C	29	II	SD	Witnessed
3C	32	IV	CHF	Transplanted †

* Representing order of entry and entry group.
† Endstage CHF (died later).
BB = beta blockade; C = control; CHF = congestive heart failure; FC = New York Heart Association functional class; SD = sudden (instantaneous) cardiac death; VF = ventricular fibrillation.

coronary heart disease. Alcohol abusers and those with other secondary cardiomyopathies (amyloidosis, hemochromatosis, etc.) were excluded. Patients with firm exclusions to β-blocker treatment (asthma, advanced heart block and allergy) were also excluded.

Treatment assignment: Treatment included low-dose β blockade (metoprolol, 12.5 mg twice a day, titrated over several days up to 50 mg twice a day as tolerated) along with standard therapy, and standard therapy alone. Standard therapy included digitalis, diuretics, vasodilators and anticoagulants as needed; however, not all patients who met entry criteria had symptoms that required digitalis or diuretic therapy. Patient randomization was performed in pairs to preserve temporal balance; the first of each pair was randomly assigned to 1 treatment; the next patient was assigned to the alternative treatment. The primary outcome variable of interest was survival. Follow-up study was performed until death or to July 1984. Cause of death, instantaneous (presumed arrhythmic) or progressive heart failure was noted.

Assessment of functional class on entry and latest follow-up was made by 1 of us (JLA) according to the New York Heart Association criteria. An alternative method of functional assessment, the San Diego questionnaire, was also used for follow-up evaluation.[7] Initial exercise testing was not always possible (because of illness and scheduling problems). However, late follow-up treadmill exercise was attempted in survivors and performed either by a local physician or in the central facility. The modified Naughton protocol formed the standard test and total exercise time the end point of interest.

Statistical analysis: Analysis of survival was made both by intention to treat and actual treatment methods. For analysis by the actual treatment method, patients unable to tolerate β blockade during initial titration were considered with the control group. Three late dropouts (all after more than 6 months of β-blocking therapy) continued to be analyzed with the treatment group. Two control patients were later crossed over to long-term β-blocking therapy because of arrhythmias and then analyzed with the treatment group.

Survival data were plotted using a Kaplan-Meier graph. Comparisons were made between groups with Mantel's extension of the Kruskal-Wallis test. A chi-square analysis was also made of survival at the end of follow-up using a 2×2 contingency table. Chi-square analysis was used to compare characteristics of the 2 groups for discrete and Student t test for continuous variables. A $p < 0.05$ (2-tailed) was taken as significant.

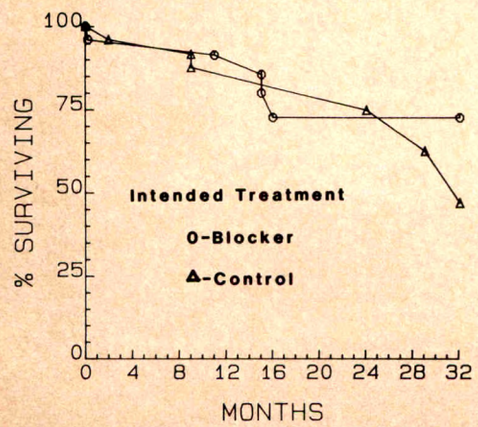

FIGURE 1. Survival curves by intention-to-treat method for control and β-blockade groups. The difference in curves is not significant.

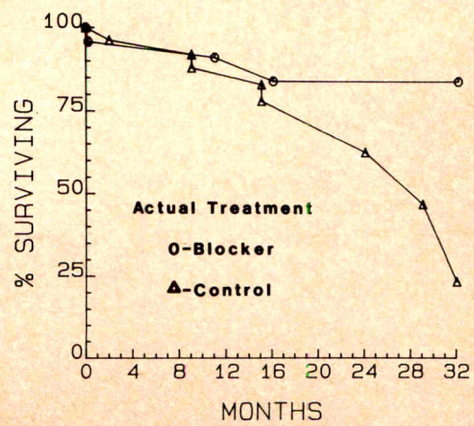

FIGURE 2. Survival curves by actual treatment method for control and β-blockade groups. The difference in curves is not significant.

TABLE III Functional Outcome Variables

Variable	Method	BB (No. of Pts)	C (No. of Pts)	p
Functional class*	Intent	2.2 ± 0.2 (25)	2.6 ± 0.1 (25)	—
	Actual	2.0 ± 0.2 (24)	2.7 ± 0.2 (26)	<0.01
Functional score† (San Diego questionnaire)	Intent	790 ± 154 (21)	1080 ± 181 (21)	—
	Actual	637 ± 136 (19)	1160 ± 173 (23)	<0.02
Heart rate at rest (beats/min)	Intent	77 ± 15 (23)	82 ± 20 (22)	—
	Actual	75 ± 12 (22)	84 ± 21 (23)	<0.06
Exercise time (min)‡	Intent	9.4 ± 1.2 (12)	8.2 ± 0.7 (16)	—
	Actual	9.3 ± 1.2 (13)	8.2 ± 0.7 (15)	—

* At last clinical evaluation (before the end of study or death) by New York Heart Association functional class.
† In survivors at last follow-up; score range = 0 to 3,000 (lowest numbers suggesting better function (see Ref. 7).
‡ Modified Naughton protocol; testing incomplete.
All values are expressed as mean ± standard error of the mean. — = difference not significant.

Results

Entry characteristics: The average age at entry was 50 ± 12 years (range 25 to 75). This age range is older than in series at transplant centers, which exclude patients older than 50 to 55 years , but is more representative of the spectrum of IDC noted clinically. Sixty-six percent of the patients were men. Entry New York Heart Association functional class averaged 2.8. Left ventricular ejection fraction at entry averaged 28%. Plasma norepinephrine was elevated. The average time from entry to evaluation at the end of the study July 1984 was identical in both groups: 23 months (range 8 to 38). Follow-up time for each subject, allowing for dropouts and deaths, averaged 19 months (range 1 to 38).

Entry characteristics by group (intention to treat) were comparable (Table I). Twenty-five were assigned to each group. The somewhat greater proportion of men in the control group was not significant.

Tolerance to beta-blocking drugs: Low-dose β blockade with metoprolol was tolerated by most patients. Initial tolerance was noted in 22 of 25 patients (88%). There were 2 late dropouts, yielding a long-term tolerance rate of 80%. The average dose of metoprolol during late follow-up was 61 mg/day (range 25 to 100). The median tolerated dose was 25 mg twice daily, but several patients used 50 mg twice daily. These doses are slightly lower than those in the Swedish experience.[1–4]

Reasons for β-blocker intolerance included 3 dropouts within the first 2 days (with 1 to 4 doses of the drug given) because of low-output syndrome in 2 and fatigue in 1. Patients who could not tolerate the drug were not rechallenged a second time. There were 2 late dropouts, at 9 and 15 months, because of progressive heart failure in 1 and pedal edema in another.

Survival trends: Survival curves for the 2 groups by the intention to treat method are presented in Figure 1. Overall, there were 5 deaths in the treatment group and 6 in the control group (difference not significant). Two patients, 1 in each group, were lost to follow-up. At 12 months, 20 patients were in the β-blockade group and 19 in the control group in ongoing follow-up. At 18 months, 10 were in the β-blockade group and 11 in the control group in ongoing follow-up. At 24 months, 7 in the β-blockade group and 7 in the control group were continuing in follow-up.

By the actual treatment method, a survival trend favoring β-blockade therapy was noted (Fig. 2). This trend became evident beyond the first year of follow-up. However, this trend did not reach statistical significance (significance level 32% by 2-tailed test, 16% by 1-tailed test).

By the intention-to-treat method, the death rate was 20% in the β-blockade group and 24% in the control group at a median of 18 months. By the actual treatment method, 13% (3 patients) of those treated with β blockade died, vs 31% (8 patients) in the control group ($p = 0.12$, χ^2) Specific deaths in the β-blockade group by actual treatment are summarized in Table IIA. The deaths occurred at 0.2, 11 and 16 months. The patients were in functional classes IV or III. The 2 in functional class IV died from progressive heart failure. In the first, who died a few days after initiating β-blockade therapy, there was concern because of a potentially negative inotropic interaction with concomitant diltiazem therapy given for angina (despite minimal coronary artery disease; spasm was questioned). In the second, β blockade was stopped 2 months before death because of progressive heart failure. In the third, death occurred suddenly 3 weeks after stopping β blockade because of peripheral edema associated with presumed progression of underlying right heart failure.

Deaths in the control group by the actual treatment method are summarized in Table IIB. These occurred at 2, 9, 9, 15, 15, 24, 29 and 32 months. Patients tended to fall into functional class IV, with 3 in functional class III or II. Five patients died suddenly and 3 died from progressive heart failure. In the first patient, the mechanism for sudden death was documented on ambulatory monitoring to be ventricular fibrillation. Patients 2 and 8 were transplanted when they became essentially moribund with failure. (Despite transplantation both died, 1 month and 3 months later.) Two of the 3 patients who had initially been intolerant of β-blockade therapy died; both were in functional class IV. Cause-specific mortality showed the strongest trend for sudden death, with 5 sudden deaths in the control group and only 1 in the β-blockade group ($p = 0.1$).

Functional outcome variables: Functional outcome trends also favored the β-blockade group (Table III).

Differences were significant by the actual treatment method, but not by the intention-to-treat method. New York Heart Association functional class at the last clinical evaluation before the end of the study or before death by the intention-to-treat method averaged 2.2 in the β-blockade group and 2.6 in the control group (difference not significant). By actual treatment, average values differed significantly, 2.0 vs 2.7 ($p < 0.01$).

A more quantitative assessment of functional class, using the San Diego questionnaire, was obtained for those who survived longer than 6 months.[7] Functional scores in this approach range from 0 to 3,000, with lower numbers suggesting better function. San Diego functional score at last evaluation averaged 790 in the β-blockade group and 1,080 in the control group ($p < 0.1$). By the actual treatment method, average values were 637 and 1,181, significantly favoring β-blocking therapy ($p < 0.02$).

Entry heart rate (mean 85 beats/min) and blood pressure (mean 118/74 mm Hg) did not differ by assigned treatment group. As expected, a lower heart rate was noted in those who received chronic low-dose β blockade on follow-up (75 ± 12 vs 84 ± 21 beats/min), but the difference did not achieve significance ($p < 0.06$). Blood pressure during therapy was similar between groups. A similar percentage of patients were given digitalis (88 and 85%), diuretic drugs (71 and 88%), vasodilators (33 and 46%), antiarrhythmic therapy (38 and 31%) and anticoagulant therapy (warfarin) (8 and 15%) in the β-blockade and control groups, respectively (actual treatment), at latest follow-up or death.

Exercise time was favorable in the β-blockade group, but follow-up was incomplete because of the large geographic distribution of referred patients, and the results were not quite significant.

Discussion

Study summary: Low-dose β blockade with metoprolol in mean doses of 25 to 50 mg twice daily was found to be tolerated both initially and on a long-term basis in 80 to 90% of patients with IDC in this prospective, controlled study. In our study, as has been observed in studies of coronary heart disease,[8,9] mortality in concurrent control patients was substantially less in prospective evaluation than had been suggested by retrospective studies. In our control patient group, a 15 to 20% per year mortality was observed, substantially lower than the 51% mortality in the first year retrospectively observed by Swedberg et al.[2] However, in patients who continued to receive long-term therapy with β blockade, a good prognosis was observed, with only a 13% mortality at a median of 18 months. This may be due to a combination of (1) protective effects of the drug, (2) a more benign course than expected for our patient group, and (3) the early selection out of high-risk patients who were intolerant of the drug. (Two of the 3 patients initially intolerant of β blockade later died from progressive heart failure.)

Previous treatment studies: In the retrospectively controlled study of Swedberg et al,[2] 24 patients treated with β blockade were compared with 13 matched historical control subjects.[2] Survival at 1 and 2 years was 83% and 69% in the β-blockade group vs 49 and 19% in the control group ($p < 0.01$). Several other studies from the same group have shown functional improvement after β-blockade therapy, including improved functional class, ejection fraction, cardiac index, apexcardiogram, and an accompanying decrease in heart rate at rest and cardiac size.[1–4] In contrast, 2 small controlled studies have questioned the positive effect of β-blockade therapy on morbidity, but the treatment periods of 30 days or less may have been too short to allow for significant treatment effects.[5,6]

Comments on mortality observations: The decreased mortality rate in our control group (15 to 20% per year) compared with that estimated from reference historical studies (25 to 50% in the first year)[2,10,11] may be a major reason for our inability to show mortality differences. In the Mayo Clinic experience (104 patients), mortality at 1 and 2 years was 32 and 46%.[10] In a recent study in 87 patients, Franciosa et al[11] observed mortality rates in severe left ventricular failure due to IDC to be 23% and 48% at 1 and 2 years. The lower control mortality rate in our study suggests that to address the mortality issue may require as many as 500 patients followed for 2 years.

A lack of a significant mortality trend may, in part, be the result of inadequately small doses. Studies in patients with coronary heart disease and hypertrophic cardiomyopathy showing improved survival have used much larger doses, averaging the equivalent of 200 mg/day or more of metoprolol.[12–14] The upward dose titration in our study was usually limited by symptoms of fatigue and dyspnea or excessive bradycardia.

Finally, the possibility of a smaller-than-expected or negligible true drug effect on survival is also consistent with our results. However, given the dismal survival results with other therapies and the lack of promising alternative approaches, it appears reasonable to pursue further the possibility of a survival advantage of β-blockade therapy.

Rationale for β-blockade therapy in dilated cardiomyopathy: The initial rationale for β blockade in IDC was to reduce tachycardia at rest.[1] Later studies indicated that an apparent beneficial effect occurred irrespective of initial heart rate.[3] The mechanism of apparent benefit is thus uncertain. Beta-adrenergic agents may exert favorable antiarrhythmic or antifibrillatory effects.[15] In coronary heart disease, several major trials have documented a beneficial effect of β-blocking drugs on survival, with the most significant reductions in mortality being in instantaneous (presumed arrhythmic) cardiac deaths.[12–15] In animal models, β-blocking drugs exert substantial antifibrillatory effects.[16] Similarly, in our study the most prominent trend was a reduction in sudden deaths. However, a trend toward a cause-specific reduction in sudden death has not been consistently noted.[2] Doses of β-blocking drugs used in the present study are also substantially less than those required for efficacy in the coronary heart disease trials.[12–14] In hypertrophic cardiomyopathy, low-dose or standard-dose β-blockade therapy has not decreased the risk of sudden death; however, substantial differences may exist in patho-

physiology between hypertrophic and dilated cardiomyopathies. Future studies should provide documentation of antiarrhythmic effects.

Two other mechanisms may be invoked to explain beneficial effects of β-blocking drugs on ventricular function. A decrease in myocardial β-adrenergic receptors (down-regulation) occurs in the failing heart, and the degree of cardiac β-receptor down-regulation can be correlated with the degree of heart failure.[17,18] Increasing levels of circulating norepinephrine and increased secretion and/or decreased norepinephrine uptake from myocardial adrenergic nerve terminals occurs, leading to increased exposure of the heart to catecholamines.[19,20] Excessive catecholamine exposure has long been known to be cardiotoxic.[20] Even lower, more "physiologic" doses of catecholamines may produce myocardial morphologic changes. Beta-blocking drugs could either prevent cardiotoxic effects of catecholamines or act to restore down-regulated, subsensitive β-adrenergic pathways to normal (or both).[18]

Limitations of the present study: This study represents a relatively small experience for establishing mortality differences, although historically controlled studies suggested the number of patients to be adequate. Lower doses of β-blocking drugs were tolerated than in some other cardiomyopathy studies.[2] The study was not blinded with respect to treatment. Patients were randomized in pairs rather than separately; this preserved temporal balance in treatment assignments. Paired observations of exercise and ventriculographic function and ambulatory monitoring could not be consistently made. However, survival observations were essentially complete and tolerance for β blockade was uniformly assessed. Clinical functional classification was also obtained in all patients.[7]

Proposal for future trials: A randomized, double-blind, multicenter study appears appropriate for further evaluation of β-blocking treatment of IDC with functional end points as a primary focus. A study of 200 to 300 patients may then yield significant results when a follow-up period of 2 years is used. Survival trends would be of additional interest. Patients should be selected for moderate to advanced disease, so as to comprise a relatively high risk group for progression. Gradual titration of the β-blocking drug should be used to achieve the highest possible dose without adverse effects. A multinational group is planning such a study.

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Two-Dimensional Echocardiographically Guided Pericardiocentesis: Experience in 117 Consecutive Patients

JOHN A. CALLAHAN, MD, JAMES B. SEWARD, MD, RICK A. NISHIMURA, MD, FLETCHER A. MILLER, Jr., MD, GUY S. REEDER, MD, CLARENCE SHUB, MD, MARK J. CALLAHAN, MD, THOMAS T. SCHATTENBERG, MD, and A. JAMIL TAJIK, MD

Pericardiocentesis guided by 2-dimensional echocardiography has been used at the Mayo Clinic since April 1980. The 2-dimensional examination localizes the pericardial fluid. Particular note is made of the place on the body wall closest to the fluid. An entry track that permits puncture of the pericardial sac without damage to any vital structure is then selected for the pericardiocentesis needle. Between April 1980 and March 1984, 132 consecutive pericardiocenteses in 117 patients were done by this technique. The volume of fluid obtained ranged from 75 to 1,700 ml (mean 650). Seventy percent of the taps were done for therapy, 21% for diagnosis, and 9% for both therapy and diagnosis. A Teflon®-sheathed "intracath" needle was used to complete 80% of the pericardiocenteses. In the other 20%, a large catheter was secondarily introduced and connected to a closed drainage system. There were no deaths related to the procedure. One symptomatic pneumothorax occurred. There were 3 minor complications. Two-dimensional echocardiographic imaging of the heart and pericardial fluid permits a safe and effective means of performing pericardiocentesis. (Am J Cardiol 1985;55:476–479)

Two-dimensional (2-D) echocardiographically directed pericardiocentesis was developed and described by members of the Mayo Clinic Echocardiographic Laboratory.[1,2] Nearly all pericardiocenteses performed at our institution since 1980 have been done in this manner. Blind percutaneous pericardial puncture has been associated with significant morbidity and mortality, and it has been recommended that this procedure be abandoned.[3–7] A safer, but more invasive, technique, subxiphoid surgical pericardiotomy, has been recommended.[8–11] We report 132 consecutive 2-D echocardiographically directed pericardiocenteses performed between April 1980 and March 1984.

Methods

Patients who had 2-D echocardiographically guided pericardiocentesis at our institution between April 1980 and March 1984 are the subjects of this report. Of the 117 patients, 52 were female and 65 were male. Fifteen of the patients had 2 separate procedures, so that 132 procedures were performed. The mean age was 50 years (range 1 to 82).

This experience represents consecutive cases of echocardiographically directed pericardiocentesis over a 4-year period. Because the number of patients increased during the study period, clinical acceptance of this new technique is implied. Pericardiocenteses performed before the echocardiographic era were not methodically catalogued. Therefore, an institutional comparison of results is not possible. We rely on published series to determine comparative risks and effectiveness (Table I).

Results

Two-dimensional echocardiographic findings: *Fluid location:* Fluid extended circumferentially in 103 instances (79%) and was loculated in 27 instances (21%).

Intrafluid strands, masses and particles: Strands were seen within the pericardial sac in 33 instances (25%). Mass lesions were noted in 4 patients (1 with *Hemophilus influenzae* infective pericarditis and 3 with metastatic malignancy). Particulate matter in great abundance was observed by 2-D echocardiography and removed by catheter in 1 infective case (*Moraxella*).

Causes of the effusion: The causes of effusion and their incidences were malignancy in 36%; unknown

From the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Manuscript received September 21, 1984; revised manuscript received November 7, 1984, accepted November 8, 1984.

Address for reprints: John A. Callahan, MD, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905.

cause in 31%; cardiac surgery in 16%; infection in 7%; and miscellaneous conditions (including trauma, rheumatoid arthritis, congestive heart failure and complications of anticoagulant therapy) in 10%. The volume of fluid obtained ranged from 75 to 1,700 ml (mean 650).

Indications for pericardiocentesis: Seventy percent of the taps were done for therapeutic reasons, 21% for diagnostic reasons and 9% for both.

Therapeutic: Symptomatic effusions (95 cases) included clinical tamponade, hypotension and dyspnea as well as "pretamponade," in which the effusion was large and caused clinical concern for the patient's safety (volume obtained, 75 to 1,700 ml, mean 650).

Diagnostic: The 26 diagnostic taps were characterized by smaller volumes (30 to 850 ml, mean 297). In 2 instances, echocardiographic contrast injections were made to verify the location of the needle cannula.[12,13]

Diagnostic and therapeutic: Both diagnostic and therapeutic indications were present in 11 cases (volume, 80 to 1,300 ml; mean 445).

Technique of 2-dimensional echocardiographically guided pericardiocentesis: *Patient positioning:* The patient was supine with the head slightly elevated or in the left lateral decubitus position in more than 90% of instances. A few patients could not assume a supine position because of dyspnea. In these patients both the echocardiographic examination and the pericardiocentesis were done with the patient sitting upright.

Puncture site: The site of needle entry was determined by 2-D echocardiographic examination. The ideal site was that at which the fluid was closest to the transducer and from which a needle track avoided the heart or any underlying vital structures. Subcostal entry was selected in 33 cases (25%), whereas in 85 cases (64%), a chest wall puncture site was chosen. In 14 of our initial cases (11%) the puncture site was not specified. The chest wall sites selected included left parasternal (11 patients), midclavicular line (6), anterior axillary line (fifth to seventh intercostal space) (61), posterior chest (1), and right parasternal (3). In 3 instances of loculated effusion, 2 entry sites were used.

Needle type: All pericardiocenteses were started with a short (2- to 4-cm) 16- or 18-gauge, Teflon®-sheathed, "intracath" needle. When the pericardial sac was entered and the first fluid was withdrawn, the Teflon sheath was advanced and the steel core was withdrawn. Seventy-eight percent of the pericardiocenteses were completed with only this small sheath.

Intrapericardial catheter: A large drainage catheter was used in 29 instances (22%). In 2 of the initial patients, only a 6 or 7Fr Teflon sheath (Cordis) was used. In 27 cases, a 6 or 7Fr pigtail catheter was inserted through the sheath into the pericardial sac. The technique involved introducing a short, flexible (0.035 mm) wire through the Teflon "intracath" sheath and then withdrawing the sheath. A dilator and introducer sheath (6Fr or 8Fr Cordis) were advanced over the wire into the pericardial sac. A pigtail catheter was introduced through this sheath. The catheter was attached to a closed system for continuous drainage, and a small amount of heparinized saline solution was injected periodically for flushing. The catheter system remained within the pericardial sac for 1 to 13 days without complication. Antibiotics were administered intrapericardially in three patients with infective pericarditis.

TABLE I Complications of Blind Percutaneous Puncture Method for Pericardiocentesis Reported in Recent Literature

First Author	Year	Procedures (n)	Complications (%)	Deaths (%)
Morin[3] (review)	1976	86		19
Krikorian[4]	1978	123		4
Kwasnik[5]	1978	34	15	0
Wong[6]	1979	52	15	2
Guberman[7]	1981	46	7	4

Complications: *Major:* No patient died. One patient (0.76%) with a previous right pneumonectomy for squamous cell carcinoma sustained a symptomatic pneumothorax during the infiltration of local anesthetic. The entry site was the anterior chest wall, near the cardiac apex. The pneumothorax was presumed to be secondary to rupture of an emphysematous bleb. A chest tube reexpanded the lung, and the pericardiocentesis was performed without incident. Three months later, a second pericardiocentesis was performed without difficulty through a subcostal entry site.

Minor: One patient had vasovagal syncope during needle insertion and refused to continue the procedure. In 2 patients, the right ventricular cavity was entered with the small sheathed needle (16 gauge) without complication. Both procedures were completed without incident. Pneumopericardium, observed in 1 patient, was without clinical consequence.

Pericardial fluid: *Amount:* One patient refused to proceed and no fluid was obtained. In 1 patient with a small effusion, no fluid was obtained. In 2 patients, only a few milliliters of fluid were obtained; 1 had thick, purulent material from which staphylococcal organisms were cultured, and the other had a clotted bloody effusion associated with a complication of anticoagulant therapy. In 2 patients, most of the pericardial effusion escaped into the pleural space, relieving tamponade. In the remaining 126 taps, the amount of fluid ranged from 75 to 1,700 ml (mean 650).

Appearance: Pericardial fluid was serous (27 patients), serosanguineous (blood-tinged or grossly bloody) (99), chylous (1), and purulent (4). Of the 99 bloody effusions, 46% were related to malignant lesions, 15% to cardiac surgery, 18% to unknown causes, 5% to infection, 4% to trauma, 4% to rheumatoid arthritis and 8% to miscellaneous conditions. Of the 27 straw-colored effusions, 33% were related to malignant lesions, 22% to cardiac surgery, 30% to unknown causes, 7% to infection, 3% to rheumatoid arthritis, 3% to congestive heart failure and 2% to miscellaneous conditions. In both groups of patients, those with straw-colored and those with bloody effusions, the miscellaneous causes consisted of myocardial infarction, trauma, rheumatoid arthritis, congestive heart failure and radiation trauma. The most unusual appearance was secondary to a gram-negative bacillus (*Moraxella*), which produced a bright yellow fluid.

Analysis: Pericardial fluid was taken under sterile conditions and uniformly sent to the microbiology

laboratory for examination for anaerobic and aerobic bacteria, tuberculosis and fungi. Among 8 taps for suspected infective pericarditis, 3 cultures were positive (beta streptococcus, *Escherichia coli* and *Hemophilus influenzae*). One patient with a negative fluid culture had a gram-negative bacillus on Gram's stain. *Moraxella* grew on a culture of pericardial material obtained at surgery 10 days later. In 3 patients with staphylococcal septicemia, cultures of pericardial fluid were negative. One patient had acute histoplasmosis with negative cultures of fluid.

Cytology: Cytologic study of the pericardial fluid was not requested in cases of trauma, cardiac surgery or known malignancy of the pericardium. It was done in 82 cases. Cytologic results were uniformly negative in the effusions unrelated to malignancy. In the effusions caused by or related to carcinoma, there were 24 positive and 24 negative cytologic findings. Among the patients with negative findings late in the course of treatment were 5 with squamous carcinoma or adenocarcinoma of the lung. Five patients had small-cell carcinoma of the lung, 5 had lymphoma, 2 had leukemia and 2 had metastatic breast cancer. Three of the patients with lymphoma had atypical lymphocytes in the pericardial fluid. One patient with metastatic breast cancer had a pericardiectomy, and no cancer could be found in the surgical specimen. Five additional patients with negative cytologic results had metastatic melanoma, osteogenic sarcoma, mucus-producing adenocarcinoma, thymoma and primary angiosarcoma of the heart. Nonmalignant pericardial disease in the cancer patients remained possible[14] but could not be proved in cases without postmortem examinations.

Surgical intervention: Twenty-nine patients had subsequent partial or complete pericardiectomy procedures for recurrent effusion, for chronic recurrent pericarditis, or for effusive-constrictive pericarditis.

Four patients had limited surgical procedures. Two had open biopsy of the pericardium and drainage of the fluid, and 2 had pericardial window procedures. All 4 patients required subsequent interventions for reaccumulated pericardial fluid. Three had 2-D echocardiographically guided pericardiocentesis and 1 had a total pericardiectomy from 2 days to 4 months after the limited surgical intervention.

Pericardiocentesis in extreme situations: Three patients had 2-D echocardiographically guided pericardiocentesis as part of a heroic lifesaving effort. In 1 patient a small amount of pericardial fluid was removed in the course of prolonged cardiopulmonary resuscitation. The outcome was not changed, but the tap was not harmful. In another patient, rupture of the heart occurred in the course of myocardial infarction. His condition improved by pericardiocentesis for several hours, but he later died. In the third patient, in whom spontaneous rupture of the ascending aorta occurred, 2 pigtail catheters were placed in the pericardial sac so that the patient could be transported to the operating room. The patient did not survive.

Discussion

The conventional, standard method of pericardiocentesis uses a subcostal, blind-puncture pericardiotomy technique essentially as described by Marfan.[15] Reports of this approach have continued to reveal significant complications and mortality.[3–7,16,17] It has been strongly suggested that the blind procedure be abandoned in favor of the safer subcostal, surgical pericardiotomy.[8–11]

Echocardiography has been established as the diagnostic procedure of choice in pericardial effusion.[18–21] The use of echocardiography in the clinical management of pericardial effusion seemed intuitive, and echocardiographic guidance for pericardiocentesis has been suggested by several investigators. In 1973, a special M-mode transducer was designed to guide the needle into the pericardial effusion.[22] Visualization of a pericardiocentesis needle by 2-D echocardiography was reported in 1978.[21] Contrast echocardiographic techniques to identify the location of the tip of the pericardiocentesis needle within the pericardial sac have been described.[12,13] Other investigators, recognizing the inherent safety of the method, have suggested using 2-D echocardiography to guide the placement of a pericardiocentesis needle.[23–26] Despite these reports, the usefulness of 2-D echocardiographically directed pericardiocentesis has not been realized. In practice, echocardiography is almost universally used to diagnose pericardial effusion, but the pericardiocentesis procedure is done by the blind percutaneous (subcostal) puncture technique or by surgical (subcostal) pericardiotomy.

We have described a technique in which the 2-D echocardiogram is used to select the optimal pericardiocentesis entry site.[1] The site chosen is that where fluid is closest to the skin and where the needle track will most effectively avoid any vital structures. Because ultrasound does not travel through air, lung tissue can be avoided. We make detailed observations with the ultrasound beam path, which is used to select the direction of the needle. The needle is passed into the fluid-containing sac without continuous echocardiographic visualization. In a few early cases, the needle was attached directly to a transducer for continuous monitoring, but we found this technique time-consuming and unnecessary. The removal of fluid is monitored intermittently by 2-D echocardiography from a remote transducer position. Because we use a Teflon-sheathed needle, we have not used electrocardiographic monitoring.[27]

The attractiveness of 2-D echocardiographically directed pericardiocentesis rests on 3 factors: It is simple, safe and effective. The simplicity has been described. The safety of the procedure is related to the instruments. The 2-D echocardiographic transducer is the operator's guide to the shortest distance from skin to fluid, allowing avoidance of the heart and other vital structures and permitting selection of the shortest and safest route to the fluid-containing space. Thus, pericardiocentesis can be performed by percutaneous needle puncture, using a short Teflon-sheathed needle, avoiding the morbidity, risk and expense of surgery and anesthesia. The effectiveness of the procedure is related in large measure to its versatility. It can easily be carried out as an emergency procedure and is complete enough to satisfy routine diagnostic needs. The small Teflon-

sheathed needle was adequate for 80% of taps. In less than 1% of cases, clot or thick, purulent material precluded effective removal of fluid.

Placement of a catheter in the pericardial sac has been described, with variations in technique, since 1955.[28] In 1966, Nordenström[29] described checking the position of an introducing system in the pericardium by visualizing small injections of contrast medium by fluoroscopy. In 1983,[30] a similar technique with a Seldinger wire technique without visualization was described. The placement of pigtail catheters by fluoroscopic guidance in children has been recommended.[31] Our common practice has been to place large drainage catheters in the pericardium by 2-D echocardiographic guidance with use of a percutaneous introducer system. A Teflon (6 or 7Fr Cordis) or pigtail catheter (5 or 7Fr) attached to a closed system was placed in 24 patients and remained in place for 1 to 13 days without complication.

Partial or complete pericardiectomy was used in this series for constrictive pericarditis, recurrent pericardial effusion, refractory infection or removal of a mass of clotted blood. In the 2-D echocardiographically directed pericardiocentesis done for therapeutic reasons (70%), the initial treatment by pericardiocentesis was effective and satisfactory in all but 3 instances. In the pericardiocenteses done for diagnosis (30%), subsequent surgical biopsy gave additional correct information in 3 cases. In this series, 2-D echocardiographically directed pericardiocentesis in the initial procedure was as effective as surgery for therapy and diagnosis.

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Magnetic Resonance Imaging of Constrictive Pericardial Disease

RENATE L. SOULEN, MD, DAVID D. STARK, MD, and CHARLES B. HIGGINS, MD

Gated magnetic resonance imaging of 5 patients with suspected constrictive pericardial disease was performed using a superconducting magnet operating at 0.35 Tesla. Results were compared with those of echocardiography and hemodynamic measurements in all patients, with chest films in 5, computerized tomography in 2 and with histologic findings in 3. Pericardial thickness exceeded 5 mm in 4 patients and was 5 mm in 1 patient. Absence of magnetic resonance signal from the thickened pericardium was observed with extensive calcific deposits, and increased intensity of the thickened pericardium was associated with inflammatory disease. Dilatation of the right atrium, venae cavae and hepatic veins, and right ventricular narrowing was observed in all patients. The ventricular septum was straight in all patients. Magnetic resonance imaging allows both measurement of pericardial thickness and depicts internal cardiac anatomy without exposure to radiation or use of contrast medium. Satisfactory imaging with a large field of view can be performed in the presence of lung disease, thoracic deformity or surgical "hardware"—conditions that limit echocardiography and computerized tomography. The inherently 3-dimensional data permit imaging in any plane without loss of resolution. Thus, magnetic resonance appears to be the noninvasive method of choice for the diagnosis of constrictive pericardial disease.

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The diagnosis of constrictive pericardial disease, and particularly its distinction from restrictive cardiomyopathy, remains a difficult clinical task.[1–5] Both entities result in restriction of ventricular filling, so it is not surprising that physical examination, noninvasive tests and even cardiac catheterization may fail to differentiate them.[1] Computerized tomography (CT), which has the capacity to define pericardial thickness, has proven valuable in this setting.[2–5] More recently, magnetic resonance imaging has also been shown to define pericardial thickness.[6] We report our experience with magnetic resonance imaging in the diagnosis of constrictive pericardial disease.

Methods

Five patients with clinical suspicion of constrictive pericardial disease were studied. One had prior cardiac surgery; 1 had prior mediastinal irradiation and chemotherapy; 1 had chronic renal failure with uremia; 2 had a positive tuberculin test result but no history of active tuberculosis. Equalization of end-diastolic pressures was found at cardiac catheterization in all 5 patients; tracking of these pressures with exercise was seen in patient 4. Prominent x and y descent in the right atrial pulse wave was seen in patients 1 and 3, and the "square-root" ventricular wave form in patient 2. Constrictive pericardial disease was considered the most likely diagnosis at the conclusion of catheterization in each patient.

Gated magnetic resonance imaging was performed using a superconducting magnet operating at 0.35 Tesla (hydrogen resonance frequency 15 MHz). The imager has been described.[7] The radiofrequency pulses and gradient pulses were synchronized to specific phases of the cardiac cycle using electrocardiographic gating. The gating technique used in our laboratory has been described in detail.[8] A spin echo pulsing sequence was used with pulse repetition interval (TR) determined by the cardiac rate and with sampling intervals (TE) of 28 and 56 ms. Imaging was performed using the multislice technique, with 5 slices obtained per sequence, each separated in time by 100 ms. The first image in each multislice series was synchronized to end-diastole and each subsequent slice corresponded to 100 ms later in the cardiac cycle. Axial images were obtained in all patients; coronal images were added in 3. Using the multislice technique, the time required to obtain a set of 5 slice is 5.5 to 8.5 minutes, depending on the subject's heart rate. Because of the long time for data acquisition, patient cooperation is important. Although respiratory motion does not usually degrade the images, patient movement during the study causes severe deterioration in image quality.

Magnetic resonance images were interpreted indepen-

From the Department of Radiology, University of California, San Francisco Medical Center, San Francisco, California. This study was supported in part by Diasonics, Inc., Milpitas, California. Manuscript received June 28, 1984; revised manuscript received September 24, 1984, accepted September 25, 1984.

Address for reprints: Charles B. Higgins, MD, Department of Radiology, University of California, San Francisco Medical Center, San Francisco, California 94143.

TABLE I Patient Data

Pt	Origin	Magnetic Resonance Imaging: Parietal Pericardium Thickness (mm)	Parietal Pericardium Intensity	Cardiac Chambers IVC	SCV	RA	LA	LV	Computed Tomography IVC	PE	TP	RA	LA	TP	PCa#
1	Surgical	5–6	N	D	0	D	N	N	D	0	+	D	N	+	0
2	Radiation	6–13		D	0	D	D	N	D	+	0	D	D	*	*
3	Uremic	6		D	D	D	N	N	D	+	+	D	N	*	0
4	Tuberculosis	11–14	N	D	D	D	N	N	D	0	+	D	N	+	+
5	? Tuberculosis	4–5	N	D	D	D	N	N	D	0	0	D	N	*	*

D = dilated; HV = hepatic veins; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; LVH = left ventricular hypertrophy; N = normal; PCa# = pericardial calcification; PE = pericardial effusion; RA = right atrium; RV = right ventricle; RVH = right ventricular hypertrophy; SVC = superior vena cava; TP = thickened pericardia; + = present or positive; 0 = absent or negative; * = not done.

dently. Data from these images were then compared with 2-dimensional and M-mode echocardiographic, hemodynamic and angiographic data in all 5 patients, with CT in 2 patients, and with operative/histologic findings in 3 patients.

Results

The causes of pericardial constriction and data from the imaging studies are listed in Table I.

Magnetic resonance: Constrictive pericarditis was characterized by pericardial thickening, which exceeded 5 mm in 4 patients and was a maximum of 5 mm in 1 patients. Thickening was diffuse, though not uniform, in 4 of these patients. One patient, who underwent prior pericardial stripping, had thickened pericardium over the right atrium only, while the right ventricle was adherent to and compressed by the sternum (Fig. 1). Intensity of the thickened pericardium varied from high, most striking in the patient with uremic pericarditis (Fig. 2), to absence of signal in areas shown by other studies to be calcified (Fig. 3). Pericardial effusion was seen only in the patient with uremia, producing a near-absent signal in contradistinction to the surrounding high-intensity pericardial image and the extensive adhesions seen coursing between the visceral and parietal layers.

Ventricular size was normal or small in all patients with constriction. Right ventricular shape was tubular and narrowed (Fig. 1, 2 and 3) in each patient. Two patients had concentric left ventricular hypertrophy (wall thickness greater than 12 mm at end-diastole), 1 patient had focal left ventricular thickening, and 1 had slight left atrial enlargement. The interventricular septum was straight in all patients. Dilatation of the cavae and hepatic veins was present in all 5 patients with constrictive pericardial disease. Pleural effusions were observed in 3 patients, bilateral in 2; the effusions showed increased intensity on the second spin echo image in each case.

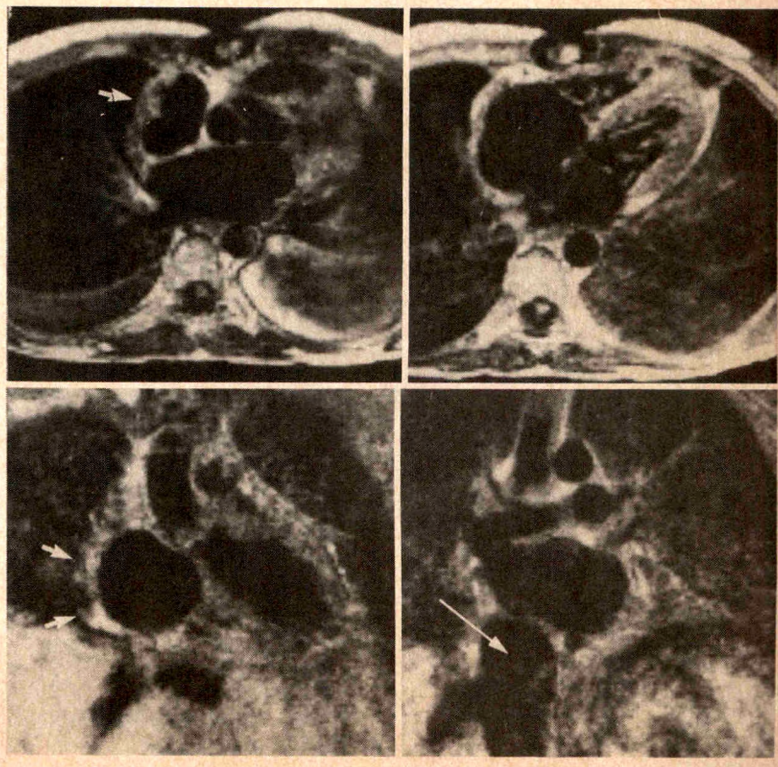

FIGURE 1. Constriction postradiation and partial pericardial stripping. Axial (**top**) and coronal (**bottom**) images show the pericardium around the enlarged right atrium to be increased both in thickness and intensity (**arrowheads**). The right ventricle is adherent to the sternum (**top right**) and somewhat cylindrical. The interventricular septum is straight. The dilated inferior vena cava (**arrow**) and hepatic veins are particularly well shown in the coronal views. Bilateral pleural effusions are present.

Comparative studies: Echocardiography identified pericardial thickening in 3 patients and pericardial fluid in 2. The magnitude of pericardial thickening in the patient with uremia was considered mild and pericardial adhesions were not found. Impaired penetration of the sound beam led to technically limited studies in the 2 patients with extensive pericardial calcification. Ventricular size was considered normal in all 5 patients with constrictive pericardial disease, although left ventricular function was depressed in 1 of these patients. Right atrial enlargement was appreciated in only 2 of these patients, although increased caliber of the inferior vena cava without respiratory variation was seen in all 5.

CT revealed thickened pericardium in the 2 patients with constrictive pericardial disease studied by CT, although evaluation of cardiac borders was obscured in 1 patient by artifacts from metallic clips. The extensive pericardial calcification in one of these patients was well demonstrated (Fig. 3).

Follow-up: Three patients underwent surgery for pericardial resection. Magnetic resonance correctly identified the pathologic entity in all 3.

Discussion

The distinction between constrictive pericarditis and restrictive cardiomyopathy is critical because the treatment of choice for the former is surgical and for the latter, medical. Pericardiectomy results in long-term improvement in 66% of patients with constrictive pericarditis.[9]

Of the functional and structural abnormalities demonstrated by noninvasive imaging techniques in constrictive pericardial disease, pericardial thickening is the prime finding that supports this diagnosis; however, thickened pericardium is not synonymous with constriction. Pericardial thickness is not reliably measured by echocardiography in the absence of fluid on both sides (pericardial and pleural)[10]; pericardial calcification produces a sonic barrier. However, echocardiography does provide important information regarding chamber size and function and respiratory variations in chamber and vena caval dimensions. It is also inexpensive and readily applied even in critically ill patients. CT permits measurement of pericardial thickness around the entire cardiac perimeter irrespective of the presence or absence of calcification, and thus is useful both in the diagnosis of constrictive pericardial disease and as a guide to adequate pericardiectomy.[2–6] The mean CT width of the thinnest portion of normal pericardium has been reported as 2.0 ± 0.6 mm in male and 2.3 ± 0.5 in female patients, with no normal measurement greater than 4 mm in either male or female patients.[11] However, small pericardial effusions are sometimes difficult to distinguish from pericardial thickening.[12] In the presence of appropriate pathophysiology, a CT measurement of 2 mm has been used by Moncada[2] and Isner[3,4] and their co-workers as the discriminating thickness between constrictive pericarditis (>2 mm) and restrictive cardiomyopathy (less than 2 mm). The pericardial thicknesses in our patients are in keeping with such classification.

Magnetic resonance, without patient irradiation, provides the same opportunity to measure pericardial thickness around the entire heart. Although nongated

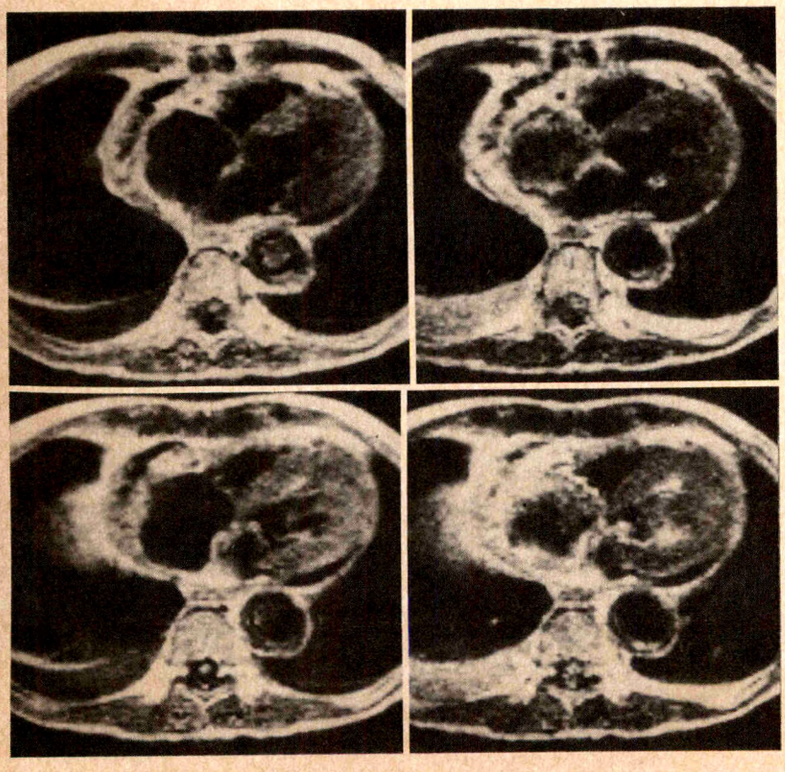

FIGURE 2. Constrictive uremic pericarditis. First (**left**) and second (**right**) spin echo images sequential axial images show irregularly thickened visceral and parietal pericardium of increased intensity, separated by low-intensity fluid, surrounding the enlarged right atrium. The second echo image shows a further increase in intensity, in keeping with a long T2. The right ventricle is normal in size, the left ventricle hypertrophied, the septum straight. Pericardial fluid is also seen behind the left ventricle, where abnormalities of the pericardium itself are less marked. Bilateral pleural effusions are present.

CT is effective for defining pericardial thickness, electrocardiographic gating is essential to adequately depict the pericardium on magnetic resonance images. The spatial resolution of magnetic resonance used in the current study was 1.7 mm, whereas that of current CT scanners is 1 mm or less. In contradistinction to the situation in CT, hemostatic clips and other metallic sequelae of cardiac surgery produce no artifacts on magnetic resonance images. Differences in signal intensity, T1 and T2 measurements can be used to characterize the thickened pericardium and have the potential for defining a specific cause. Strikingly high intensity has been reported in patients with uremic pericarditis[6] and attributed to increased tissue water content associated with an inflammatory process. The histologic findings in 1 of our patients support this hypothesis. The cause of the increased intensity in patient 2 is uncertain. The near-absent signal in the inner pericardial rim of patient 4 correlates very well with the extensive calcification seen in the same areas on CT (Fig. 3) and is in keeping with the paucity of mobile protons in this tissue. However, because fibrotic tissue also produces low-intensity signals, magnetic resonance intensity cannot match CT for the detection of pericardial calcification.

Focal deformity of the right ventricular contour and acute angulation of the distal interventricular septum on CT scans have been described by Doppman et al[5] as characteristic of constriction, but these findings have not been corroborated by others[2–4] and were not seen in our patients. Instead, constriction was manifested by right ventricular narrowing, resulting in a tubular-shaped chamber of modest size, in contrast to a disproportionately dilated right atrium, inferior vena cava and hepatic veins.

Thus, magnetic resonance imaging permits the

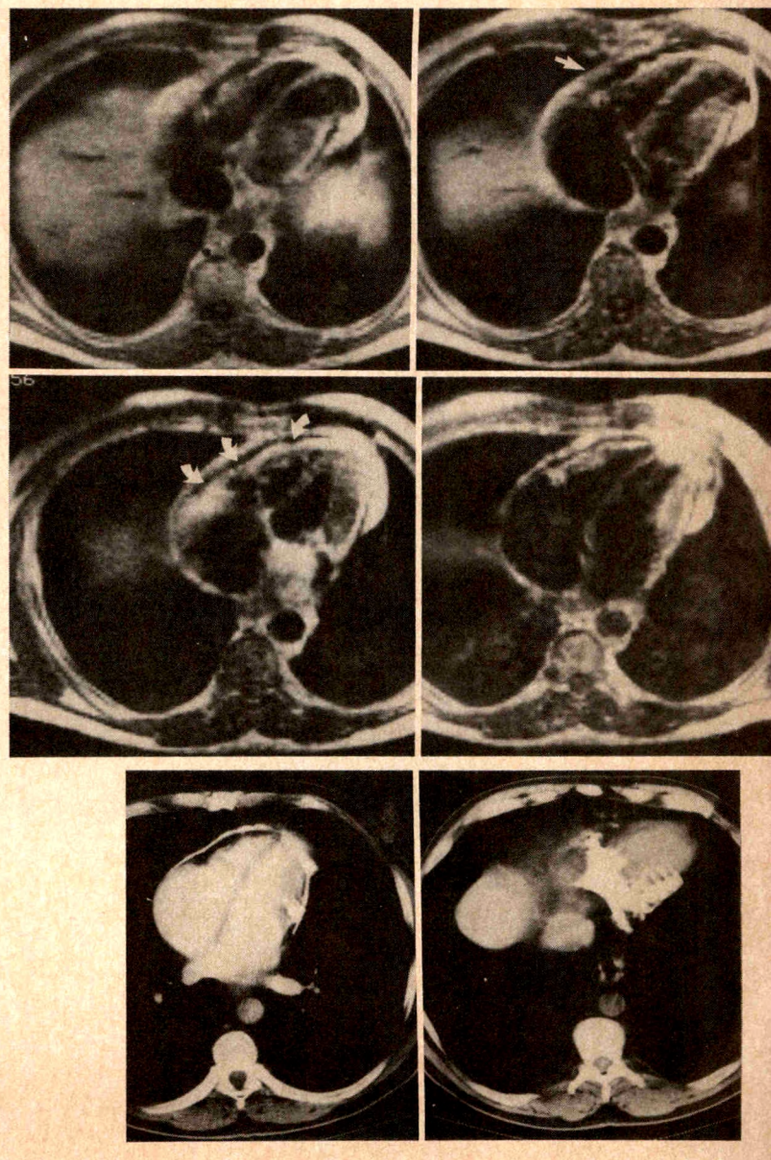

FIGURE 3. Calcific constrictive pericarditis. Multilevel axial magnetic resonance images (**top** and **middle**) reveal a thickened pericardium characterized by 2 layers. A wide, low-intensity rim (**arrowheads**) just above the epicardial fat is attributed to the calcification, well shown on computed tomography (CT). Extension of this calcification into a region of focal left ventricular wall thickening is clear on both magnetic resonance (**middle right**) and contrast-enhanced CT scan (**lower right**); the calcification in the posterior atrioventricular groove seen on CT (**lower left**) was not appreciated on magnetic resonance. A peripheral layer of medium intensity (**arrow**) is best seen adjacent to the right ventricle (**top right**). Both ventricles are narrowed and elongated (**top left** and **right, middle** and **lower right**); the septum is straight; the right atrium is dilated.

measurements of pericardial thickness and also displays the alterations in the size of cardiac chamber indicative of pericardial constrictive disease. This early experience suggests that magnetic resonance may be the preferred imaging technique for suspected pericardial constrictive disease.

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The King of Hearts: Analysis of 23 Patients with Hearts Weighing 1,000 Grams or More

WILLIAM C. ROBERTS, MD, and MICHAEL J. PODOLAK, BSE*

Certain clinical and morphologic features are described in 23 patients in whom the heart at necropsy weighed at least 1,000 g (mean 1,106). The heart weight to body weight ratio ranged from 1.2 to 2.7 (normal 0.40). The 23 patients were derived from examination of the hearts of 7,671 patients with various cardiovascular disorders over a 25-year period. The massive cardiomegaly was the result of aortic regurgitation in 14 patients (61%): isolated in 8, associated with mitral regurgitation in 4, and with ventricular septal defect in 2. Three others (13%) had combined aortic valve stenosis and aortic regurgitation and 1 patient (4%) had mitral stenosis and regurgitation and mild aortic stenosis. Four patients (17%) had hypertrophic cardiomyopathy, and 1 patient (4%) had ventricular septal defect with mitral stenosis. They were 20 to 64 years old (mean 42) and 21 (91%) were men. Four patients at necropsy had 1 or more major coronary arteries narrowed more than 75% in cross-sectional area by atherosclerotic plaques, and only 4 patients had grossly visible left ventricular (LV) scars, 2 of whom had insignificant coronary narrowing. Examination of electrocardiograms in 17 of the 23 patients disclosed that Sokolow-Lyon criteria for LV hypertrophy was achieved in only 12 patients (71%) and Romhilt-Holt QRS voltage criteria faired even worse. Total 12-lead QRS voltage was more than 175 mm (10 mm = 1 mV) in 16 patients (94%) and it was more than 250 mm in 13 patients (76%). Total 12-lead QRS voltage in 17 patients ranged from 140 to 601 mm (mean 323). Measurement of the sum of the 12-lead QRS voltage may be quite useful in diagnosing LV hypertrophy by electrocardiogram.

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The upper limit of the normal heart weight in women is about 350 g and for men, about 400 g. Hearts that weigh 1,000 g or more* in human beings are rare. During the past 25 years one of us (WCR) has examined at necropsy the hearts of 23 patients in whom the heart weighed at least 1,000 g (>2.5 times normal weight). Certain clinical and morphologic findings in these 23 patients are described in this report.

Methods

From July 1, 1959, to July 30, 1984, the hearts of 7,671 patients with cardiovascular disease were examined at the National Institutes of Health by 1 of us (WCR). The file of each was reexamined and the records of those in whom the heart weight was recorded as at least 1,000 g were pulled. Thirty-two patients had hearts that weighed more than 1,000 g recorded in the necropsy protocol. Upon review of the records and on reexamination of most of the hearts it was apparent that the weights in 9 of the 32 patients were inaccurately recorded because ascending aorta or parietal pericardium or other tissues were still attached to the heart, and although the hearts weighed more than 900 g, they weighed less than 1,000 g. Thus, 23 patients remained in whom the heart itself weighed at least 1,000 g. In 21 of the 23 patients the weights were those recorded by 1 of us (WCR). In each, the weight was that obtained after the heart had been fixed in 10% formalin for about 48 hours, after the main right and left pulmonary arteries, ascending aorta (2 cm cephalad to the sinotubular junction), all parietal pericardium and all intracardiac clot or thrombus had been removed from the heart itself. The scale used to weigh most of the hearts was a Mettler P1210, a scale with a range from 10 mg to 1,200 g. A different scale was used for the 4 hearts that weighed more than 1,200 g.

The clinical and morphologic records in all 23 patients were then examined. The hearts in 15 of the 23 patients were reexamined.

Results

The data obtained in the 23 patients are recorded in Tables I, II and III. The patients were 29 to 64 years old

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received September 7, 1984; revised manuscript received and accepted October 5, 1984.

* Freshman Student, Duke University Medical School, Durham, North Carolina.

Address for reprints: William C. Roberts, MD, Building 10A, Room 3E-30, National Institutes of Health, Bethesda, Maryland 20205.

* To better sense the feeling of 1,000 g, the June 1, 1984, issue of *The American Journal of Cardiology* weighed 967 g. It included 459 pages (279 editorial and 180 advertising).

TABLE I Clinical and Morphologic Observations in the 23 Patients with Hearts Weighing 1,000 Grams or More

Pt	Age (yr), Race & Sex	Cardiac Disorder	LV (s/d) (mm Hg)	SA (s/d) (mm Hg)	LV-SA psg (mm Hg)	RV (s/d)	AR by AA cine (0–4+)	MR by LV cine (0–4+)	CI	AVR	MVR	Interval Op to Death	Ht. (cm)	HW (kg)	BW (g)	HW/BW (%)	No. AV Cusps	LV F	No. CAs >75%
1	30WM	AR	140/33	140/38	0	50/9	4+	0	2.5	+	0	37 mo	167	1,200	79	1.5	3	0	0
2	32BM	AR	...	215/45	...	...	...	...	...	0	0	...	165	1,030	68	1.5	3	0	0
3	39WM	AR	170/16	175/50	0	34/6	4+	1+	4.5	+	0	25 days	170	1,100	63	1.7	3	0	0
4	39WM	AR	140/20	140/38	0	32/5	4+	1+	2.8	0	0	...	183	1,010	85	1.2	2	0	1
5	41BM	AR	120/12	120/75	0	24/8	3+	0	2.6	+	0	21 mo	190	1,270	109	1.2	3	0	0
6	43WM	AR	...	180/80	...	...	...	...	...	+	0	60 mo	183	1,020	87	1.2	3	0	0
7	44WM	AR	140/10	145/40	0	...	4+	...	...	+	0	2 days	...	1,050	...	...	2	0	0
8	51WM	AR	152/38	158/46	0	56/12	3+	1+	2.0	+	0	0	178	1,010	80	1.3	3	0	2
9	29WM	AR + MR	130/14	140/40	0	45/10	4+	2+	1.9	+	+	3 days	165	1,040	52	2.0	3	0	0
10	45WM	AR + MR	144/18	152/45	0	35/7	4+	2+	1.8	+	+	10 days	175	1,040	74	1.4	3	0	0
11	50WM	AR + MR	118/18	140/63	0	46/15	2+	4+	...	+	+	0	185	1,005	91	1.1	3	+	0
12	62BM	AR + MR	195/18	210/40	0	45/6	4+	2+	2.0	+	0*	52 mo	183	1,230	71	1.7	3	+	1
13	29WM	AR + VSD	155/20	170/70	0	70/4	4+	...	...	+†	0	12 mo	185	1,360	93	1.5	3	0	0
14	34WM	AR + VSD	168/22	145/48	23	68/6	1+	...	...	+†	0	1 day	178	1,150	58	2.0	3	0	0
15	53WM	AR + AS	120/36	100/40	20	60/10	1+	0	...	+	0	12 mo	183	1,100	70	1.6	2	0	0
16	56WM	AR + AS	190/14	130/75	60	24/8	2+	...	...	+	0	53 mo	186	1,100	57	1.9	2	0	0
17	60WM	AR + AS‡	...	100/60	...	...	...	...	...	0	0	...	173	1,050	55	1.9	2	+	1
18	64WM	MS§ + MR + AS	120/12	110/60	10	50/9	...	3+	3.9	0	+	76 days	176	1,055	73	1.4	3	0	0
19	20WF	HC	158/10	108/57	50	40/7	...	3+	3.9	0	0	...	161	1,250	47	2.7	3	+	0
20	32WM	HC	...	95/60	...	...	...	...	...	0	0	...	...	1,200	...	...	3	0	0
21	33WM	HC	105/25	117/70	0	33/7	0	0	2.7	0	0	...	179	1,020	82	1.2	3	0	0
22	45WF	HC	...	...	...‖	...	...	...	...	0‖	0‖	144 mo	...	1,150	...	...	3	0	0
23	30BM	VSD + MS¶	...	160/110	...	...	...	...	...	0	0	...	...	1,005	78	1.3	3	0	0

* Aortic valve replacement 53 months before death; mitral valve replacement 2 days before death.
† Closure of ventricular septal defect at same time.
‡ Although the mitral valve was neither stenotic nor incompetent, its anulus contained heavy (4+/4+) calcific deposits.
§ Left atrial to left ventricular mean diastolic gradient = 13 mm Hg.
‖ This patient also had obstruction to left ventricular outflow and partial ventricular septotomy-septectomy was performed 144 months before death.
¶ Parachute mitral valve (single papillary muscle syndrome).

AA = ascending aorta; AR = aortic regurgitation; AS = aortic valve stenosis: AV = aortic valve; AVR = aortic valve replacement; BW = body weight; CAs = coronary arteries; cine = cineangiogram; CI = cardiac index; F = grossly visible fibrosis; HC = hypertrophic cardiomyopathy; Ht = height; HW = heart weight; LV = left ventricle or ventricular; MR = mitral regurgitation; MS = mitral stenosis; MVR = mitral valve replacement; RV = right ventricle; SA = systemic artery; s/d = peak systole/end-diastole; VSD = ventricular septal defect.

TABLE II Electrocardiographic Findings in 17 Necropsy Patients with Hearts Weighing 1,000 Grams or More

Pt	Interval ECG to Death	Cardiac Disease	VR (bpm)	Intervals QRS (sec)	Intervals P-R (sec)	QRS Voltage I	II	III	aVR	aVL	aVF	V_1	V_2	V_3	V_4	V_5	V_6
1	37 mo	AR	54	0.12	0.24	10	9	15	6	13	11	50	50	52	37	10	16
2	1 day	AR	125	0.16	0.08	18	11	6	10	4	7	27	32	27	21	7	9
3	40 days	AR	75	0.12	0.28	29	13	21	22	27	9	50	58	72	42	21	50
4	75 days	AR	64	0.12	0.20	12	8	15	9	12	10	30	56	52	37	24	50
8	3 days	AR	73	0.10	0.20	15	12	19	10	16	14	27	52	39	37	38	32
9	8 days	AR-MR	112	0.12	0.22	16	10	20	11	18	12	42	86	82	46	43	28
10	11 days	AR-MR	90	0.12	...*	3	8	9	4	5	8	6	38	48	46	23	16
11	2 days	AR-MR	115	0.11	...*	3	14	14	7	7	13	13	38	40	44	40	20
12	52 mo	AR-MR	105	0.16	...*	16	20	32	10	21	26	30	60	68	60	18	41
13	12 mo	AR-VSD	102	0.08	0.18	12	15	25	12	18	18	31	68	72	68	28	30
14	9 days	AR-VSD	74	0.12	0.28	5	16	17	9	10	16	12	46	70	70	70	24
15	12 mo	AR-AS	73	0.12	0.20	13	10	16	10	13	7	39	50	40	28	26	35
16	53 mo	AR-AS	64	0.12	0.19	24	17	11	20	17	7	21	23	14	20	20	15
18	79 days	AR-MR-MS	55†	0.08	...†	4	6	5	5	3	5	6	12	25	34	20	15
19	41 mo	HC	56	0.12	0.08	34	37	23	30	33	74	70	40	52	64	74	70
21	4 mo	HC	76	0.10	0.16	21	23	27	16	22	20	30	60	54	40	56	36
23	6 mo	VSD-MS	71	0.12	0.32	31	14	35	17	31	22	17	13	22	29	44	33
	Mean			0.12	0.20	16	14	18	12	16	16	30	46	49	43	32	31

Pt	Total 12-Lead QRS Voltage	S V_1	S V_2	R V_5	R V_6	Largest S V_1–V_3 (mm)	Largest S V_1–V_3 (Lead)	Largest R V_4–V_6 (mm)	Largest R V_4–V_6 (Lead)	Largest R in 6 Limb Leads (mm)	Largest R in 6 Limb Leads Lead	Largest S in 6 Limb Leads (mm)	Largest S in 6 Limb Leads Lead	R I	S III
1	279	50	50	3	16	50	V_1	16	V_6	10	aVL	10	III	8	10
2	179	23	28	2	9	27	V_3	9	V_6	11	II	10	aVR	15	2
3	414	50	56	8	42	68	V_2	42	V_6	30	I	23	aVR	30	21
4	315	27	54	23	47	54	V_2	47	V_6	12	I	10	III	12	10
8	311	26	46	33	34	46	V_2	34	V_6	14	I	11	III	14	11
9	414	34	82	14	25	82	V_2	25	V_6	15	I	13	III	15	13
10	214	5	36	11	14	42	V_3	14	V_6	8	III	5	aVL	2	0
11	253	14	34	34	38	34	V_2	34	V_5	13	III	7	aVR	3	0
12	402	30	56	8	39	62	V_3	39	V_6	20	aVL	28	III	16	28
13	397	30	64	10	30	66	V_3	30	V_6	15	II	13	III	11	13
14	365	9	45	12	21	70	V_3	21	V_6	11	III	8	III	3	8
15	287	30	46	24	35	46	V_2	35	V_6	13	I	14	III	13	14
16	209	20	22	20	15	20	V_1	20	V_5	23	I	19	aVR	23	9
18	140	6	11	14	15	20	V_3	15	V_6	6	II	2	aVL	3	0
19	601	26	0	60	60	26	V_1	60	V_5,V_6	50	aVF	24	aVF	30	23
21	405	29	54	52	36	56	V_2	54	V_5	22	II	16	aVR	21	10
23	308	6	3	21	15	6	V_1	21	V_5	32	III	26	aVL	9	0
	323	24	40	21	28	45		30		18		14		13	10

* Atrial fibrillation: †atrioventricular junctional rhythm.
AR = aortic regurgitation; bpm = beats per minute; HC = hypertrophic cardiomyopathy; MR = mitral regurgitation; MS = mitral stenosis; VR = ventricular rate; VSD = ventricular septal defect.

(mean 42); 21 (91%) were men and 2 (9%) were women. Cardiac conditions producing the massive cardiomegaly were: (1) pure *aortic regurgitation* (AR) in 14 patients (isolated in 8, associated with mitral regurgitation [MR] in 4 and with ventricular septal defect [VSD] in 2); (2) *combined aortic stenosis (AS) and AR* in 3; (3) *hypertrophic cardiomyopathy* in 4; (4) *combined mitral stenosis (with MR) and AS* in 1 patient; and (5) *VSD with mitral stenosis* (parachute mitral valve) in 1. Of the 8 patients with isolated pure AR, the origin of the valve disease was infective endocarditis that healed in 2[1] (patients 4 and 6, Table I) (Fig. 1), congenitally bicuspid aortic valve that never was the site of infection in 1 (patient 6),[2] uncertain in 2 (patients 1 and 5), rheumatic in 1 patient (patient 2), ankylosing spondylitis in 1 (patient 3),[3] and syphilis in 1 (patient 8) (Fig. 2).[4] Of the 4 patients with combined AR and MR, the cause was rheumatic in 3 (patients 9, 11 and 12) and infective endocarditis that healed in 1 (patient 10) (Fig. 3). The AR in the 2 patients with VSD (nos. 13 and 14) resulted from prolapse of 1 of the 3 aortic valve cusps, with superimposed infective endocarditis that healed in 1 of the patients (no. 14) (Fig. 4 and 5). One patient (no. 14) with AR plus VSD also had a small (20-mm Hg) peak systolic pressure gradient between left ventricle and systemic artery (Fig. 5). Two patients (nos. 15 and 16) had congenitally bicuspid aortic valves causing combined aortic valve stenosis and regurgitation (Fig. 6)[5]; the stenosis was the dominant hemodynamic lesion in 1 (patient 17) and he had a bicuspid aortic valve (Fig. 7). The cause of the combined mitral and aortic valve stenosis in patient 18 was rheumatic. The hypertrophic cardiomyopathy in patients 19 to 22 was congenital in origin (Fig. 8). Patient 23 obviously had congenital heart disease (Fig. 9).

Electrocardiograms were available for examination in 17 patients (Table II, Fig. 1, 3, 5 and 6). Twelve had had valve replacement operations; the electrocardio-

TABLE III Recommended or Modified Electrocardiographic Criteria for Determining Left Ventricular Hypertrophy as Applied to 17 Patients with Hearts at Necropsy Weighing More than 1,000 Grams

No.	QRS Complex Measured	Value Considered Upper Limit of Normal (mm)	No. (%) of 17 Patients Above Normal Limit
1a	$SV_1 + RV_5$ or V_6 (larger)	35	12 (71)
b	$SV_1 + RV_5$ or V_6 (larger)	40	11 (65)
2a	SV_1 or V_2 (larger) + RV_5 or V_6 (larger)	35	15 (88)
b	SV_1 or V_2 (larger) + RV_5 or V_6 (larger)	40	14 (82)
3a	SV_1 or V_2 (larger) + RV_6	35	15 (88)
b	SV_1 or V_2 (larger) + RV_6	40	13 (76)
4a	$SV_2 + RV_5$	35	14 (82)
b	$SV_2 + RV_5$	40	14 (82)
5a	Deepest $SV_1 - V_3$ + tallest $RV_4 - V_6$	35	14 (82)
b	Deepest $SV_1 - V_3$ + tallest $RV_4 - V_6$	40	13 (76)
c	Deepest $SV_1 - V_3$ + tallest $RV_4 - V_6$	45	13 (76)
d	Deepest $SV_1 - V_3$ + tallest $RV_4 - V_6$	50	13 (76)
6a	Tallest R + deepest S in any V lead	35	14 (82)
b	Tallest R + deepest S in any V lead	40	14 (82)
7a	Deepest $SV_1 - V_3$	25	14 (82)
b	Deepest $SV_1 - V_3$	30	12 (71)
8a	Tallest $RV_4 - V_6$	25	9 (53)
b	Tallest $RV_4 - V_6$	30	8 (27)
9a	Deeper SV_1 or V_2	25	14 (82)
b	Deeper SV_1 or V_2	30	12 (71)
10a	Tallest RV_5 or V_6	25	9 (53)
b	Tallest RV_5 or V_6	30	8 (47)
11	$RV_6 > RV_5$	≤ 1	13 (76)
12a	Tallest limb-lead R + deepest limb-lead S	15	15 (88)
b	Tallest limb-lead R + deepest limb-lead S	20	12 (71)
13a	$R_1 + S_3$	15	12 (71)
b	$R_1 + S_3$	20	10 (59)
14a	Tallest limb-lead R	10	14 (82)
b	Tallest limb-lead R	15	6 (35)
15a	Deepest limb-lead S	10	10 (59)
b	Deepest limb-lead S	15	6 (35)
16	R_1	10	11 (65)
17	S_3	10	7 (41)
18a	Total 12-lead QRS voltage	175	16 (94)
b	Total 12-lead QRS voltage	200	15 (88)
c	Total 12-lead QRS voltage	225	13 (76)
d	Total 12-lead QRS voltage	250	13 (76)

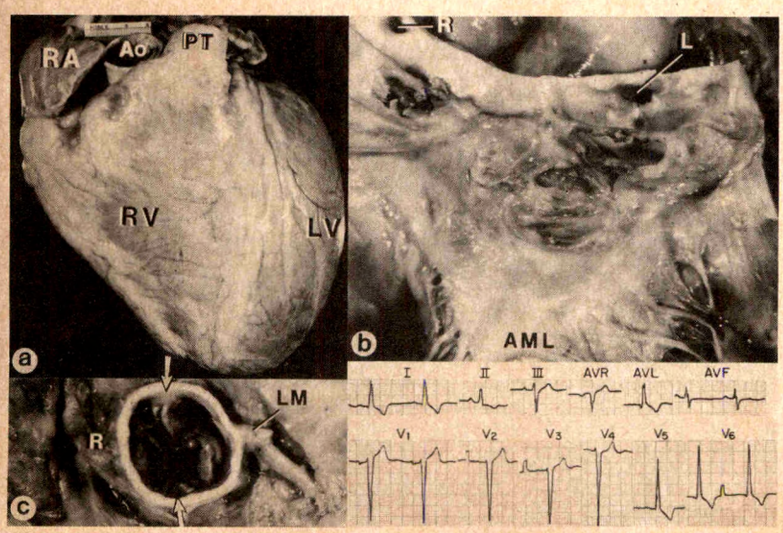

FIGURE 1. Patient 4 in Table I. Heart, weighing 1,010 g, and electrocardiogram from a 39-year-old man (A69-254) who had active infective endocarditis on a bicuspid aortic valve at age 24 years and aortic regurgitation thereafter. He refused operative treatment. He died suddenly while playing golf. **a,** exterior of heart. Ao = ascending aorta; LV = left ventricle; PT = pulmonary trunk; RA = right atrium; RV = right ventricle. **b,** opened aortic valve. Each cusp is perforated and the margins of the perforations contain small calcific deposits. AML = anterior mitral leaflet; L and R = left and right coronary ostia. **c,** congenitally bicuspid aortic valve from above. The **arrows** designate the 2 commissures. LM = left main and R = right coronary artery. The QRS voltage in the precordial leads is enormous. A strain pattern is present.

gram analyzed was recorded within the month preceding operation. Seven of these 12 patients died within 76 days (median 3) of operation; the other 5 patients died 12, 12, 37, 52 and 53 months (mean 33) after operation. In the latter 5 patients electrocardiograms were available for examination 12, 7, 22, 52 and 31 months (mean 25), respectively, after valve replacement.

A single QRS complex was measured in each lead in the 17 patients (Fig. 10). The total 12-lead QRS voltage ranged from 140 to 601 mm (mean 323) (10 mm = 1 mV); in 16 patients (94%) this voltage was more than 175 mm and in 13 (17%), more than 250 mm. In 5 patients with isolated severe AR, the total 12-lead QRS voltage ranged from 179 to 414 mm (mean 300); in 4 patients with combined AR and MR, it was 214 to 414 (mean 321); in 2 patients with AR plus VSD, it was 365 and 397 mm; in 2 patients (nos. 15 and 16) with AR plus AS, it was 209 and 287 mm, and in 2 patients with hypertrophic cardiomyopathy, it was 405 and 601 mm. The mean QRS voltage in each of the 12 leads in each of the 17 patients was 27 mm. The individual and mean QRS amplitudes in each of the 12 leads in the 17 patients are

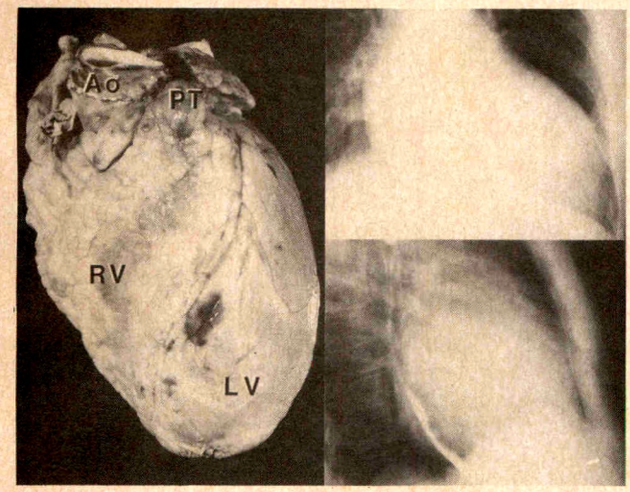

FIGURE 2. Patient 8. **left,** exterior view of heart weighing 1,010 g from a 51-year-old man (A68-8) with chronic aortic regurgitation from syphilis. The enormousness of the heart is apparent from the posteroanterior (**upper right**) and lateral (**lower right**) radiographs. Abbreviations as in Figure 1.

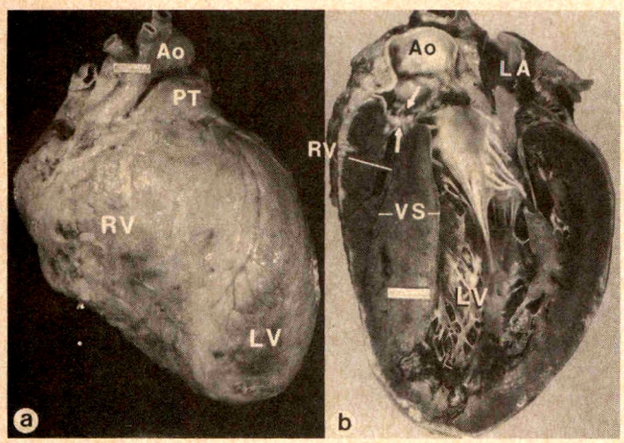

FIGURE 4. Patient 13. Heart from a 29-year-old man (A71-197) with ventricular septal defect (VSD) complicated by aortic regurgitation. He died 1 year after closure of the VSD and replacement of the aortic valve. The aortic regurgitation resulted from prolapse of 1 of the 3 aortic valve cusps. **a,** exterior view of heart. The heart weight (1,360 g) was determined after most of the ascending aorta and pulmonary trunk had been excised. **b,** longitudinal cut of heart. The **arrows** point to the site of the previous VSD. The caged-ball prosthesis has been removed. A thrombus is present in the left ventricular apex. VS = ventricular septum; other abbreviations as in Figure 1.

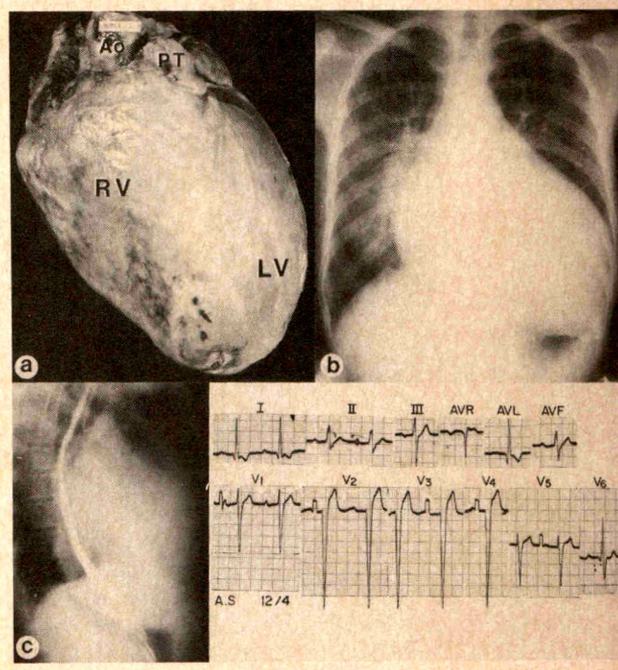

FIGURE 3. Patient 9. Heart weighing 1,040 g (**a**), chest radiographs (**b** and **c**) and electrocardiogram from a 29-year-old man (A68-3) with combined pure aortic and mitral regurgitation of rheumatic origin. Leads V_1 to V_5 are at one-half standard. Abbreviations as in Figure 1.

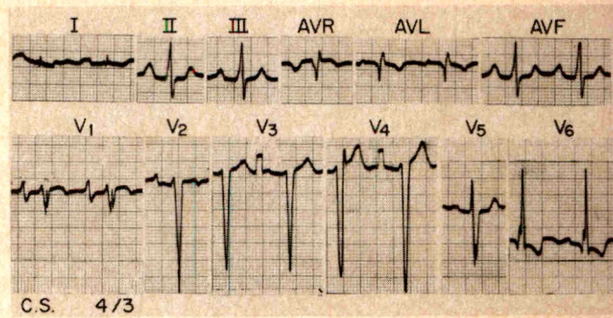

FIGURE 5. Patient 14. Electrocardiogram from a 34-year-old man (A64-92) with aortic regurgitation (AR) complicating ventricular septal defect (VSD). The heart weighed 1,150 g. He had active infective endocarditis at age 21 years and severe aortic regurgitation thereafter. A large perforation was present in the prolapsed aortic valve cusp at the time of closure of the ventricular septal defect and aortic valve replacement 1 year before death. The QRS voltage in the preoperative electrocardiogram is enormous. Leads V_3 and V_4 are at one-half standard.

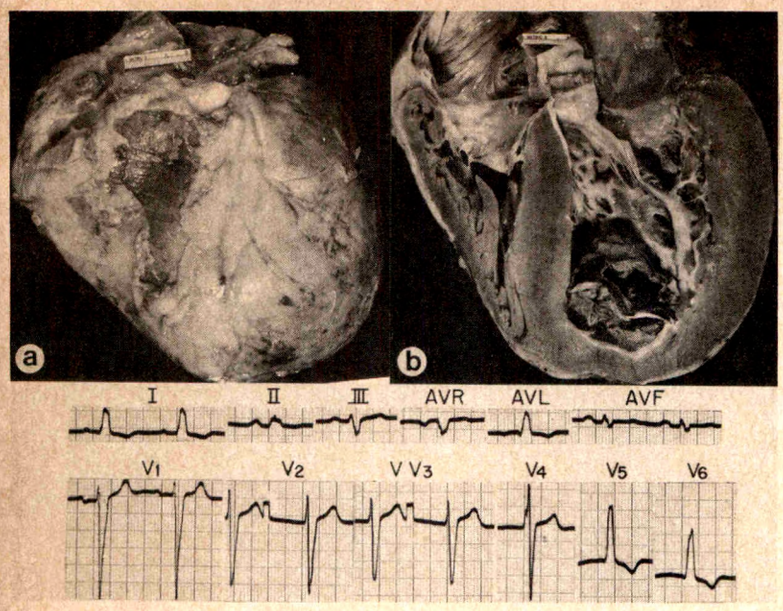

FIGURE 6. Patient 15. Heart and electrocardiogram in a 53-year-old man (A70-54) who developed active infective endocarditis on a congenitally bicuspid aortic valve with severe aortic regurgitation (AR) thereafter. At catheterization before aortic valve replacement, a 20-mm Hg peak systolic pressure gradient was present between left ventricle and aorta and aortic root cineangiogram disclosed 4+/4+ AR. He died 1 year after aortic valve replacement. **a,** exterior view of heart, which weighs 1,100 g. **b,** longitudinal view. The prosthetic aortic valve has been excised. A thrombus is present in the left ventricle. The electrocardiogram shows high QRS voltage in the precordial leads and a strain pattern. Leads V_2 and V_3 are at one-half standard.

listed in Table II. The highest mean 12-lead QRS voltage occurred in lead V_3 (49 mm), next in V_2 (46 mm), next in V_4 (43 mm), and it was lowest in lead aVR (12 mm). The QRS mean voltage in leads V_5 and V_6 were similar (32 and 31 mm).

Various electrocardiographic QRS voltage criteria for left ventricular hypertrophy and the frequency of their occurrence in the 17 patients are summarized in Table III.[6–10] A few criteria have been slightly modified to allow the number designating the upper limit of normal to end in a 0 or a 5 and to allow the elevated value to always be greater than a certain number rather than equal to or greater than a certain number. Of the 18 criteria analyzed, only 1 upper-limit number was evaluated in 3, two values were analyzed in 13, and 4 values in 2. Thus, a total of 37 values were analyzed for the 18 criteria: 36 were measurements in millimeters of QRS voltage and 1 was a ratio.

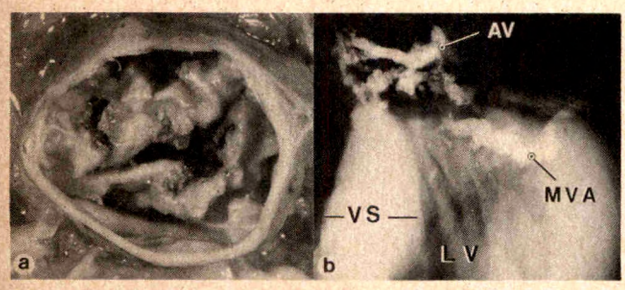

FIGURE 7. Patient 17. Stenotic and heavily calcified, bicuspid aortic valve and calcified mitral valve anulus in a 60-year-old man (A71-14). Congestive heart failure developed about a year before death. Electrocardiogram (not available for reexamination and therefore not included in the analysis of 17) disclosed atrial fibrillation, complete right bundle branch block and Q waves in leads II, III, aVF and V_4 to V_6. This patient had a large anterior wall transmural left ventricular scar. **a,** severely stenotic and mildly incompetent aortic valve from above. **b,** radiograph of heart showing calcium in both aortic valve (AV) and mitral valve anulus (MVA). The mitral valve functioned normally. LV = left ventricular cavity; VS = ventricular septum.

The QRS voltage criterion with the highest positive frequency was the sum of the voltage of the QRS complexes in all 12 leads being more than 175 mm (94%); this total QRS voltage was more than 200 mm in 15 (88%) and more than 250 mm in 13 of the 17 patients (17%).

Several recognized QRS voltage criteria for LV hypertrophy were met in 15 of the 17 patients (88%): (1) sum of the S wave in V_1 or V_2 (larger) plus the R wave in V_5 or V_6 (larger) being >35 mm; (2) sum of the S wave in V_1 or V_2 (larger) plus R in V_6 being >35 mm; and (3) sum of the tallest limb-lead R wave plus the deepest limb-lead S wave being >15 mm.

The S-wave amplitude in lead V_1 ranged from 5 to 50 mm (mean 24); the R-wave amplitude in lead V_5 ranged from 2 to 60 mm (mean 21) and in lead V_6, from 9 to 60 mm (mean 28). The sum of the S wave in lead V_1 and the larger of the R waves in either V_5 or V_6 (Sokolow-Lyon index) ranged from 19 to 92 mm (mean 55), and in 12 patients (71%) it was more than 35 mm. The deepest S wave in leads V_1 to V_3 ranged from 6 to 82 mm (mean 45) and in 14 patients (82%) it was more than 25 mm. The deepest S wave in leads V_1 to V_3 was in lead V_1 in 4 patients (24%), in lead V_2 in 6 patients (35%), and in V_3 in 7 patients (41%). The average S-wave amplitude was higher in lead V_2 than V_1 (40 vs 24 mm).

The largest R-wave amplitude in leads V_4 to V_6 ranged from 9 to 60 mm (mean 30), and in 9 patients (53%) it was more than 25 mm; the largest R wave in V_4 to V_6 was in lead V_5 in 5 patients (29%) and in lead V_6 in 12 patients (71%). The mean height of the R wave was higher in lead V_6 than in V_5 (28 vs 21 mm), and the R wave in V_6 was higher than the R wave in V_5 in 13 patients (76%).

Of the 17 patients with electrocardiograms available for analysis, 13 were in sinus rhythm, 3 had atrial fibrillation and 1 patient had atrioventricular junctional rhythm. The PR interval was prolonged (>0.20 second) in 5 of the 13 patients (38%) with sinus rhythm. The

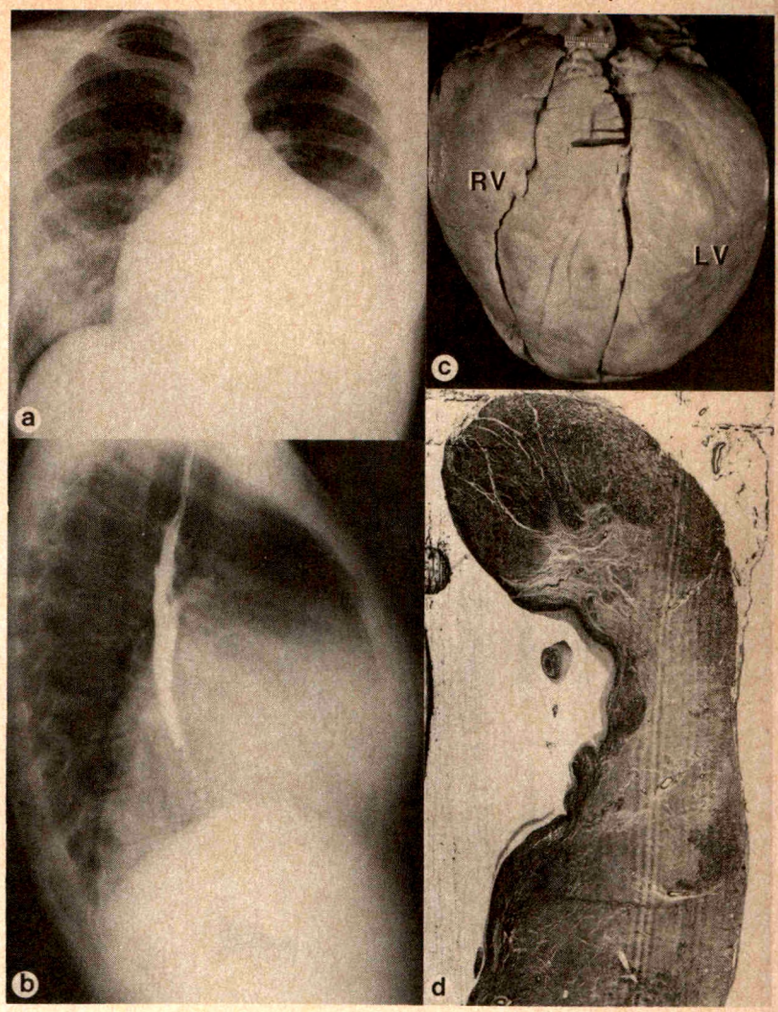

FIGURE 8. Patient 19. **a** and **b,** chest radiographs 4 years before death; **c,** heart weighing 1,250 g; and **d,** longitudinal section of left ventricular free wall showing a healed myocardial infarct in a 20-year-old woman (A72-197) with hypertrophic cardiomyopathy. She weighed 47 kg. The myocardial infarct likely was the result of inability of the normal epicardial coronary arteries to adequately supply the huge mass of myocardium. LV = left ventricle; RV = right ventricle.

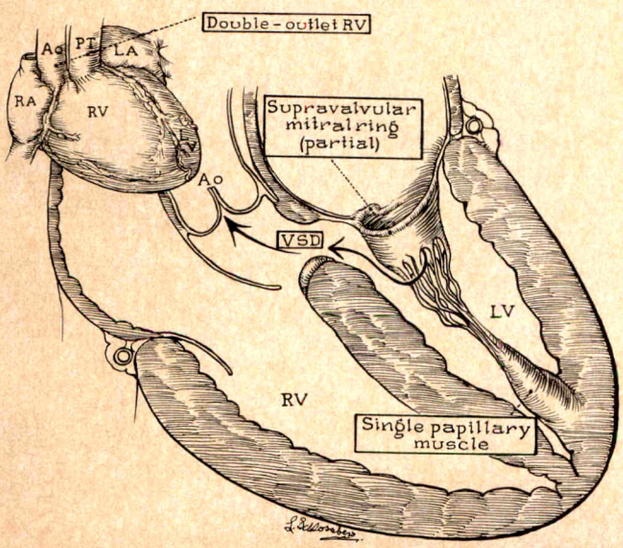

FIGURE 9. Patient 23. Diagram of heart from a 30-year-old man (83-02-106) with congenital mitral stenosis, ventricular septal defect (VSD) and double-outlet right ventricle (RV). The heart weight 1,005 g. Ao = aorta; LA = left atrium; LV = left ventricle; PT = pulmonary trunk; RA = right atrium.

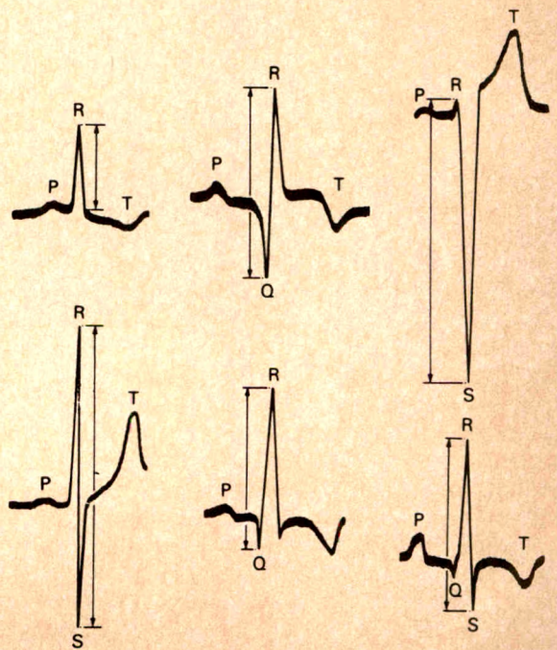

FIGURE 10. Various QRS complexes showing how each was measured.

QRS width was 0.12 second or longer in 12 patients (71%).

Cardiac valve operations were performed in 16 of the 23 patients (70%): isolated aortic valve replacement in 9, simultaneous aortic plus mitral valve replacements in 3, aortic valve replacement plus closure of ventricular septal defect in 2, isolated mitral valve replacement in 1 patient and partial ventricular septotomy-septectomy (for hypertrophic cardiomyopathy) in 1 (patient 22). Eight of the 16 patients died within 90 days (median 3) of operation and the other 8 died 12 to 144 months (mean 49) after operation.

At necropsy, the hearts weighed 1,005 to 1,360 g (mean 1,106); in 15 patients the range was 1,005 to 1,100 g and in 8 it was 1,150 to 1,360 g. The body weight (available in 20 patients) ranged from 47 to 109 kg (mean 74). The percent of body weight contributed by heart weight ranged from 1.1 to 2.7 (mean 1.6) (normal 0.38 to 0.46 [mean 0.40] for women and 0.42 to 0.46 [mean 0.43] for men). Four patients (17%) had congenitally bicuspid aortic valves.

One or more of the 4 major coronary arteries (right, left main, left anterior descending and left circumflex) were narrowed more than 75% in cross-sectional area in 4 of the 23 patients (17%), only 1 of whom had as many as 2 arteries so narrowed. Grossly visible left ventricular scars were found in 4 patients (17%), 2 of whom were among the 4 patients with severe (>75%) coronary narrowing. Two patients (nos. 11 and 12) had small, posterior wall, transmural (> inner one-half of the wall) left ventricular scars. Patient 17 had a large anterior wall scar and a narrowed single coronary artery. Patient 20 had extensive transmural left ventricular scarring with normal extramural coronary arteries; this 20-year-old woman had a 1,250-g heart and she weighed only 103 pounds. We believed that the myocardial ischemia was the result of the myocardial mass "outgrowing" the ability of the coronary bed to perfuse it.

Discussion

The present study includes the largest number of patients heretofore reported with hearts weighing 1,000 g or more. The present study differs from previous ones concerning massive cardiomegaly in that the weights of the hearts, with 2 exceptions, were those recorded by 1 person (WCR) and only after the attachments (great arteries, parietal pericardium, intracardiac clot, and so forth) to the heart had been removed. All previous studies including more than 1 patient with massive cardiomegaly have used heart weights recorded in necropsy protocols, an inaccurate method for obtaining accurate information.[11] Through the years one of us (WCR) has received many hearts originally stated to weigh more than 1,000 g, but after removing the noncardiac attachments the weight was usually less.

The present study demonstrates that there are relatively few conditions that cause the heart to weigh 1,000 g or more. Among our 23 patients, 14 (61%) had *pure "volume" lesions:* isolated AR in 8, AR plus MR in 4, and AR plus VSD in 2. Five patients (22%) had *combined "pressure" and "volume" lesions:* 3 had AS (2 of whom also had considerable AR and 1 [patient 17] of whom had mild AR); 1 patient had mitral stenosis with severe MR; and 1 had mitral stenosis with VSD. Four patients (17%) had *hypertrophic cardiomyopathy*, 2 of whom had peak systolic pressure gradients at rest between left ventricle and aorta. Thus, with the exception of hypertrophic cardiomyopathy and an occasional patient with combined valvular stenosis and regurgitation, it is usually the patient with AR with or without MR or VSD who has a heart that weighs 1,000 g or more.

Several other investigators have observed hearts weighing 1,000 g or more at necropsy. Cabot,[12] in 1926, described 7 men, aged 19 to 52 years (mean 33) whose hearts were recorded as weighing 1,000 to 1,328 g (mean 1150). Although he stated that "chronic pericarditis with mediastinitis produces the largest hearts . . ." all 6 of his patients with "chronic pericarditis and mediastinitis" had valvular heart disease (AR in 4 patients AS in 1 patient and probably both AR and MR in 1). His only patient without "chronic pericarditis and mediastinitis" had syphilitic AR. Golden and Brams[13] described 9 patients (8 men), aged 28 to 57 years (mean 46), with hearts recorded as weighing 1,000 to 1,475 (mean 1,131). The cause of the severe cardiomegaly was AR in 6 (isolated in 5 and associated with MR in 1), combined aortic and mitral valve stenosis in 1 patient and systemic hypertension in 2. Rosenow and Smith[14] reported 3 men, aged 40, 46 and 58 years, with hearts that weighed 1,017, 1,100 and 1,170 g, respectively. Two patients had AS (1 with associated MR) and 1 had systemic hypertension. Strong and Munroe[15] reported 8 patients (7 men), aged 28 to 62 years (mean 43), with hearts recorded as weighing 1,000 to 1,750 g (mean 1,108). The cause of the cardiomegaly was AR in 5 patients, (isolated in 4 and associated with MR in 1), AS in 1 patient and systemic hypertension in 1. Pena[16] reported 15 men, aged 25 to 65 years (mean 49), who had hearts that were recorded as weighing 1,000 to 2,000 g (mean 1,158). The cause of the cardiomegaly was AR in 6 patients (isolated in 4 and associated with MR in 2), isolated MR in 1 patient and systemic hypertension in 8. One of the latter patients also had acromegaly, and his heart weighed 1,525 g. The heart recorded as weighing 2,000 g was in a patient with MR; his blood pressure was 130/70 mm Hg. (We doubt the accuracy of this weight; it is unlikely that the heart can enlarge more than 5 times normal size.) Several investigators in this century have described a single patient in whom the heart weighed 1,000 g or more.[17–24] The cause of the enlargement was AS in 2,[19,22] AR or MR or both in 2,[18,23] cardiac amyloidosis in 1,[24] acromegaly in 1[17] and uncertain cause in 2.[20,21]

Thus, the reports of others cited herein also indicate that valvular heart disease, primarily AR, is the most frequent cause of massive (≥1,000 g) cardiomegaly. In contrast to our study, however, systemic hypertension was mentioned as a cause of massive cardiomegaly. We suspect this cause is unlikely and that more likely the heart was not weighed accurately. Examination by 1 of us (WCR) of hearts of 756 patients with systemic hy-

TABLE IV Frequency of Hearts Weighing 1,000 Grams or More Among Necropsy Patients with Cardiac Disease Studied in the Pathology Branch, National Heart, Lung, and Blood Institute*

	No. of Patients	Number Heart Weight ≥ 1,000 g
Valvular heart disease		
Aortic stenosis (AS)	355	3 (1%)
Mitral stenosis (MS)	216	0
AS + MS	167	1
Aortic regurgitation (AR)	138	8 (6%)
Mitral regurgitation (MR)	122	0
MS + AR	70	0
MR + AR	49	4 (8%)
AS + MR	23	0
Tricuspid stenosis + MS ± AS	29	0
Hypertrophic cardiomyopathy	171	4 (2%)
Ventricular septal defect†	30	3‡
Idiopathic dilated cardiomyopathy	165	0
Amyloid heart disease	57	0
Systemic hypertension	756	0
Acromegaly	9	0
Massive obesity (body weight >176 kg)	12	0
Totals	2369	23

* Excludes coronary heart disease.
† Without associated right ventricular outflow obstruction and age older than 15 years.
‡ Two had associated severe aortic regurgitation and 1 had associated congenital mitral stenosis (parachute mitral valve).
Abbreviations as in Table I.

pertension during life disclosed none weighing 1,000 g or more (Table III). Likewise, among 57 hearts of patients with cardiac amyloidosis extensive enough to cause cardiac dysfunction, none weighed 1,000 g or more (Table IV).[25] Although acromegaly has been reported as causing a human heart to weigh 1,000 g or more,[16,17,26] 1 of us (WCR) has not observed such an occurrence among 9 patients with acromegaly studied at necropsy (Table III).[27] Although in persons of normal weight and without heart disease, heart size is proportional to body weight,[28] such is not the case in patients with massive obesity.[29] Warnes and Roberts[29] studied 12 patients at necropsy whose body weight was more than 176 g (>300 lbs) and their hearts weighed 380 to 990 g (mean 616). No one, to our knowledge, has reported a heart in a human being weighing 1,000 g or more on the basis of massive obesity alone.

Our report is the first to demonstrate hypertrophic cardiomyopathy to be a cause of massive (≥1,000 g) cardiomegaly. Of our 4 patients, 2 were women, the only 2 women among our 23 patients. As a group, the largest hearts among our 23 patients were the 2 with AR plus VSD (mean 1,255 g) and the next largest were the 4 with hypertrophic cardiomyopathy (mean 1,155 g), a weight greater than that of the 8 patients with isolated AR (mean 1,086 g), the 4 patients with AR plus MR (mean 1,079 g), or the 4 with AS (mean 1,100 g). It is not surprising that hypertrophic cardiomyopathy has not been described previously as a cause of massive (≥1000 g) cardiomegaly because the last article on causes of massive cardiomegaly was in 1962 (by Pena[16]) and hypertrophic cardiomyopathy was described only 4 years earlier (1958).[30] Our study also is the first to demonstrate massive cardiomegaly in a patient with VSD. Two of our 3 patients with VSD, however, had AR and the third also had congenital mitral stenosis. It is doubtful that VSD as an isolated anomaly can cause cardiomegaly to the extent that the heart could weigh 1,000 g or more.

The frequency of massive (≥1,000 g) cardiomegaly among certain groups of cardiac patients studied at necropsy by one of us (WCR) is summarized in Table IV. Of the 138 patients with clinically isolated pure AR, 8 (6%) had hearts weighing at least 1,000 g; of the 49 patients with combined pure AR plus MR, 4 (8%) had massive cardiomegaly. Of the 355 patients with AS with or without AR, only 3 (1%) had hearts weighing 1,000 g or more. Of the 171 patients with hypertrophic cardiomyopathy studied at necropsy, 4 (2%) had massive cardiomegaly. None of the 152 patients with idiopathic dilated cardiomyopathy had massive cardiomegaly.[31] Of the hundreds of patients with atherosclerotic coronary heart disease unassociated with another condition and studied at necropsy by one of us (WCR), none had hearts weighing 1,000 g or more.

All but 1 previous study on patients with hearts weighing 1,000 g or more referred to herein were published before 1950 or before 12-lead electrocardiograms became routine (rather than 3 or 6-lead electrocardiograms). The 1 study on huge hearts since 1950 did not describe electrocardiographic findings.[16] Thus, our study is the first to examine 12-lead electrocardiograms in patients in whom the heart weighed 1,000 g or more. Total 12-lead QRS voltage in adults with hearts of normal weight has not been determined but 175 mm (10 mm = 1 mV) would probably be a reasonable upper limit. Of our 17 patients in whom electrocardiograms were available, 16 (94%) had total 12-lead QRS voltage more than 175 mm and in them it ranged from 179 to 601 mm (mean 335); 13 of the 16 patients had total 12-lead QRS voltage more than 250 mm. The largest voltage occurred in 2 patients with hypertrophic car-

diomyopathy (405 and 601 mm), and next in the 2 patients with AR plus VSD (365 and 397 mm). In the 1 patient (no. 18) in whom the total 12-lead QRS voltage was less than 175 mm, the total voltage was 140 mm. This patient had diffuse LV hypokinesia on angiography with an ejection fraction of 23%, insignificant aortic valve disease, severe mitral stenosis and MR, and a large thrombus in the body of the left ventricle (not included in the cardiac weight). Thus, the amount of left ventricle hypertrophy in this patient was much less than in the other 16 patients.

The Sokolow-Lyon index[6] was not a sensitive indicator of left ventricular hypertrophy. The sum of S_{V_1} and R_{V_5} or $_{V_6}$ (larger) was more than 35 mm in only 12 (71%) of the 17 patients, and in these 12 it ranged from 40 to 92 (mean 67); in the 5 patients in whom this index was normal (≤35 mm), it ranged from 19 to 32 (mean 26). The Romhilt-Estes[7] QRS voltage criteria for left ventricular hypertrophy faired worse although it is recognized that non-voltage criteria also were used by these 2 investigators. The patients fulfilling their QRS voltage criteria were as follows: (1) largest R wave in any of the 6 limb leads of 20 mm or more, 6 patients (35%); (2) largest S wave in any of the 6 limb leads of 20 mm or more, 6 patients (35%); (3) largest S wave in leads V_1 to V_3 of 25 mm or more, 14 patients (82%); (4) largest R wave in V_4 to V_6 of 25 mm or more, 10 patients (59%). The criteria for left ventricular hypertrophy examined by Scott et al[8] yielded the following: (1) R wave in lead I and S wave in lead III of more than 25 mm, 7 patients (41%); (2) R wave in V_5 or V_6 of more than 26 mm, 9 patients (53%). (3) R wave plus S wave in any precordial lead of more than 45 mm, 13 patients (76%). Griep[9] and, later, Holt and Spodick[10] used the R_{V_6}:R_{V_5} voltage ratio for diagnosing left ventricular hypertrophy. They found that when the R-wave voltage in lead V_6 was larger than that in lead V_5 that left ventricular hypertrophy was usually present. In 13 of our 17 patients (76%), the R_{V_6}:R_{V_5} ratio was >1. Thus, despite using several ECG criteria for diagnosis of hypertrophy in hearts known to be enormous (≥1,000 g), voltage criteria for left ventricular hypertrophy was present only 35 to 88% of the time (Table III). Measuring total 12-lead QRS voltage appears to be useful in diagnosing left ventricular hypertrophy by electrocardiogram.

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Detection of Platelet Deposition at the Site of Peripheral Balloon Angioplasty Using Indium-111 Platelet Scintigraphy

CHRISTOPHER F. POPE, MB ChB, MICHAEL D. EZEKOWITZ, MRCP, PhD,
EILEEN O. SMITH, BS, STANLEY RAPOPORT, MB ChB,
MORTON GLICKMAN, MD, H. DIRK SOSTMAN, MD, and BARRY L. ZARET, MD

Restenosis after balloon angioplasty may be mediated through platelet deposition at the site of arterial dilatation. The purpose of this study was to determine whether platelet deposition at the site of dilatation could be detected using indium-111 platelet scintigraphy. Fifteen patients, aged 60 ± 9 years, with iliac or femoral (n = 12), renal artery (n = 2) or distal aortic (n = 1) stenoses were studied. All patients received intravenous heparin at the time of dilatation. Labeled platelets containing 471 ± 65 μCi indium-111 were injected 0.25 to 4 hours after dilatation and 1 to 24 hours after imaging. In 11 of 12 patients with iliac and femoral dilatations, focal uptake was demonstrated at the angioplasty site. In 4 patients (2 patients with renal, 1 patient with iliofemoral, and 1 with distal aortic stenoses), uptake at the dilatation sites was not detected. This preliminary study indicates that despite intravenous heparin, platelets accumulate at sites of balloon dilatation. Platelet scintigraphy may be useful in predicting sites of future narrowing after angioplasty and may be used to test the efficacy of antiplatelet therapy in retarding restenosis.

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Percutaneous transluminal balloon angioplasty has become an important therapeutic option for the treatment of both peripheral and coronary atherosclerotic disease. The procedure is relatively nontraumatic and has significant cost advantages compared with surgery.[1] Initial patency rates at 1 month of approximately 86% for iliac and 73% for femoral angioplasty have been reported.[1] However, restenosis after successful dilatation continues to be the major limitation of this procedure. It is estimated that after 1 year, restenosis occurs in 23% of iliac and 44% of femoral dilatations, and that these rates increase to 37% and 71%, respectively, at 5 years.[1] For coronary angioplasty the restenosis rate at 3 to 6 months is estimated to be as high as 36%.[2]

The pathogenesis of restenosis after angioplasty is unclear. Histologic studies at both light and electron microscopic levels demonstrate platelets at sites of dilatation.[3,4] Our hypothesis is that platelets, by virtue of a number of possible mechanisms including vascular spasm, thrombosis and accelerated atherosclerosis, play a major role in promoting restenosis.[5] As a first step in testing this hypothesis, it must be determined whether platelet deposition at the site of dilatation can be reliably demonstrated in vivo in man. To this end, indium-111 platelet scintigraphy was used. This technique is effective in visualizing platelet deposition at sites of atherosclerotic peripheral vascular disease and on the surface of artificial arterial grafts.[6–9] The peripheral circulation, as opposed to the coronary circulation, was chosen for this initial study because the relatively low background blood pool activity and simple geometry provide an ideal anatomic substrate in which to visualize arterial platelet deposition with the scintigraphic technique.

From the Yale University School of Medicine, New Haven, and West Haven Veterans Administration Medical Center, West Haven, Connecticut. Manuscript received July 9, 1984; revised manuscript received October 9, 1984, accepted October 11, 1984.

Address for reprints: Michael D. Ezekowitz, MD, PhD, Yale University School of Medicine, 333 Cedar Street, 87 LMP, New Haven, Connecticut 06510.

Methods

Patients: All patients selected clinically for peripheral angioplasty were considered eligible for the study. Written informed consent was obtained. Fifteen patients (8 men and 7 women, aged 60 ± 9 years, mean ± standard deviation) were studied. Twelve had femoral or iliac vessel stenoses, 2 had renal artery stenoses, and 1 patient had a lesion in the distal abdominal aorta.

Angioplasty: All arterial punctures were performed through the common femoral artery. Serial dilatations at the stenotic sites were achieved using standard balloon catheters. (Medi-Tech Inc.). Intraarterial heparin (5,000 IU) was administered immediately after the catheter was passed across

the stenosis. After angioplasty, anticoagulant regimens were ordered individually based upon the preference of the physician performing the procedure. No patient received antiplatelet therapy before the procedure. After the procedure 8 patients received intravenous heparin for 8 to 24 hours. An additional patient was administered 40% Rheomacrodex® intravenously at a rate of 500 ml/hour for 3 days. Six patients received long-term therapy (aspirin, 650 mg/day, 4 patients; Persantine®, 75 mg/day and coumadin 5 mg/day, 1 patient; and Persantine alone, 75 mg/day, 1 patient).

Labeling and imaging: Platelets were labeled with 471 ± 61 μCi of indium-111 according to previously described techniques[10–12] and injected 1.2 ± 1.4 hours after dilatation. Ten-minute anterior views of the sites of dilatation and catheter insertion were obtained 13 ± 10 hours after injection of the labeled platelets and subsequently for as long as 5 days. All patients underwent imaging within 24 hours of injection of labeled platelets. Additional images were obtained during the imaging period: 1 image in 5 patients, 2 images in 1 patient, 4 in 3 patients and 5 in 3 patients; in 3 patients only 1 image was obtained. A positive image was defined as an area of increased activity at a site other than the catheter insertion site. A large-field-of-view scintillation camera, fitted with a medium-energy collimator and set with symmetric 20% windows centered on both peaks of indium-111, was used. Patients undergoing renal artery dilatation were imaged in the anterior, posterior and anterior-oblique views. Initial images contained total counts ranging from 169,000 in the pelvis to 54,000 in the thigh. After the catheter puncture site was identified, images were read and then correlated with the angiograms.

Results

In 11 of 12 patients undergoing iliac or femoral angioplasty, areas of intense activity indicating platelet deposition (Fig. 1 and 2), were seen. After 24 hours these remained essentially unchanged. All corresponded to sites of dilatation. In 4 patients uptake at dilatation sites was not detected: in both patients with renal artery stenoses, 1 patient with a distal aortic stenosis and 1 with an external iliac stenosis. The initial platelet images showed increased activity at the puncture site (Fig. 1 and 2) in 12 of 14 patients imaged. The puncture site was not imaged in 1 patient (not in the field of view), and showed no activity in 2 others. Figure 1 demonstrates the value of obtaining sequential images. Initial images obtained 4 hours after dilatation and 3.5 hours after injection of the platelet suspension provided much less convincing evidence of platelet deposition then did the images obtained 20 hours later. Two factors may contribute to this observation: the continual uptake of platelets by the damaged vessel and the diminution of blood pool activity or both these factors working in concert. The images in Figure 2 are from a patient in whom clinically apparent hematoma occurred as a complication of the procedure. This was clearly visualized on the scintigram. Although endothelial damage at the puncture site probably coexisted with the hematoma, it is unlikely that this contributed significantly to the increased activity visualized. Thus, uptake at the puncture site should not automatically be interpreted as representing platelet deposition or thrombosis. In the image in Figure 1 a clinically apparent hematoma was not seen, but the puncture site was clearly visualized. The source of the increased activity may represent endothelial damage. However, clinically silent perivascular extravasation of blood may occur and cannot be excluded as a cause of the increased activity. Figure 2 is an example of inhomogeneous uptake in a patient who underwent dilatation of a long stenosis. There is diffuse

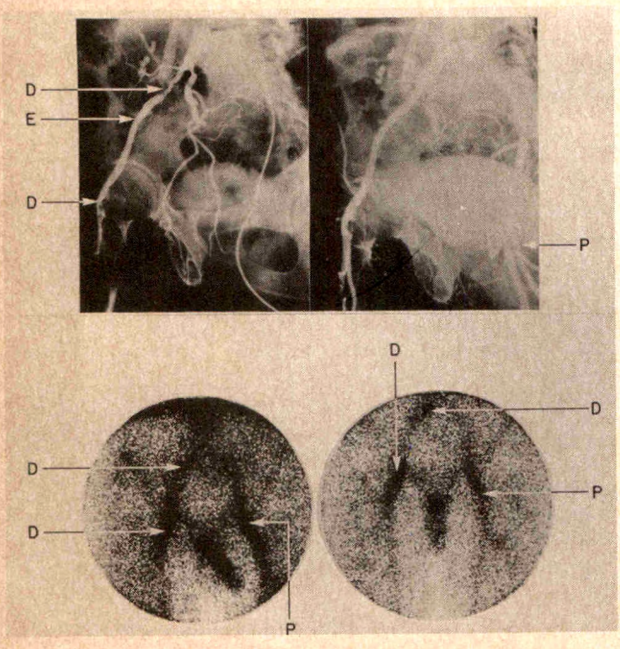

FIGURE 1. Top, pre- (**left**) and post- (**right**) angioplasty angiograms. **Bottom,** corresponding indium-111 images acquired 4 and 24 hours after angioplasty. D = dilatation sites; E = external iliac artery; P = puncture site with associated hematoma. The 24-hour image, with the reduced blood pool activity, clearly shows areas of increased platelet uptake.

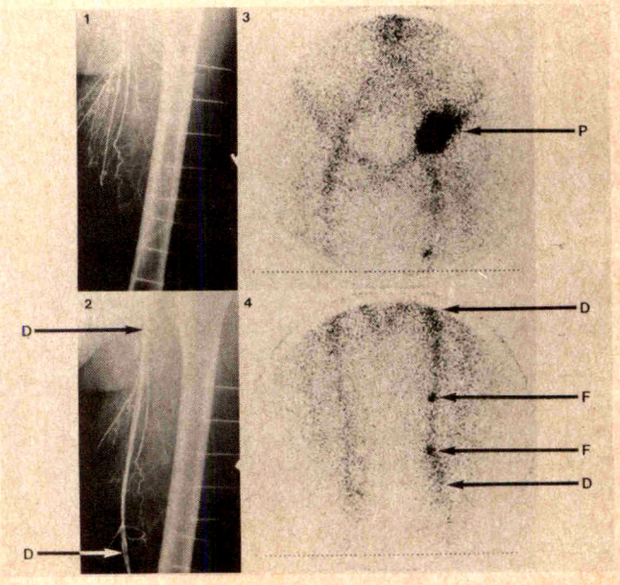

FIGURE 2. Panels 1 and **2,** pre- and postangioplasty angiograms. **Panels 3** and **4,** platelet scintigraphic photos obtained 14 hours after injection. The **arrows** (D) mark the proximal and distal extent of the long stenosis that was dilated. **Panel 4,** diffuse uptake between the 2 markers. In certain areas (F) uptake was more pronounced. A 6 × 6 cm hematoma complicated the procedure. P = puncture site.

uptake along the whole length of the portion of the vessel that was dilated. At sites marked F, increased focal uptake was seen. These areas presumably correspond to the sites of most marked endothelial disruption.

Discussion

After balloon angioplasty, areas of intense indium-111 activity, corresponding to dilatation sites, occur in a high percentage of patients. Because the indium-111 label is not released when labeled platelets undergo adhesion or aggregation,[13] the conclusion that these areas of increased activity represent sites of platelet accumulation is reasonable. Platelet imaging therefore may be used as a marker of early thrombosis or platelet deposition. Platelet deposition at the site of angioplasty in experimental animals has also been documented morphologically.[3] The stimulus for platelet deposition most probably involves exposure of subendothelial collagen (a potent initiator of platelet aggregation) by balloon dilatation and resultant endothelial disruption, fissuring and even medial dissection. Platelet deposition may be a mechanism of accelerating atherosclerosis and restenosis, since platelets release platelet-derived growth factor which by itself can induce myointimal proliferation.[5] Despite the administration of heparin and streptokinase during the angioplasty procedure, and the subsequent administration of antiplatelet and anticoagulant agents during the imaging period, 11 of 15 patients in this study had platelet uptake at sites of dilatation. This is consistent with previous reports demonstrating the lack of effect of heparin, streptokinase and aspirin on platelet adhesion,[14–16] the presumed mechanism of early platelet deposition at sites of dilation. Cunningham et al[17] recently showed that the pretreatment of men undergoing angioplasty with aspirin resulted in the inhibition of uptake of indium-111 labeled platelets. In this study none of the patients were pretreated with aspirin. Those who did receive aspirin did so within 24 hours after angioplasty; no effect was seen. Conflicting results have also been reported in animals. Intravenous aspirin administered 1 hour before angioplasty in the dog had no detectable effect in preventing platelet uptake at the site of dilatation.[18] In contrast, Wu et al[19] reported that small doses of aspirin inhibited platelet uptake in the catheter-injured rabbit aorta, whereas higher doses (150 mg/kg) did not.[19] These differences may reflect species specificity.

The only patient who failed to show platelet uptake at the angioplasty site in the iliac or femoral group had Rheomacrodex® (40% at 500 ml/hour intravenously for 3 days) administered immediately after dilatation. This agent interferes with platelet adhesion.[20] However, until further investigation confirms this effect, this isolated observation should be interpreted with caution. Two patients with renal artery angioplasty demonstrated no focal activity at these sites. Adjacent splenic and hepatic activity may have obscured the activity from the renal artery, and thus it is uncertain whether these patients had true-negative study results. Thus, due to anatomic rather than physiologic considerations, platelet scintigraphy may have limited application in the study of renal angioplasty. This observation was made in another recent study.[21] In the 2 patients in whom uptake at the puncture site was not detected, uptake at the sites of dilatation were similarly absent, suggesting that the platelet preparation was rendered nonphysiologic as a result of cellular damage during labeling. An alternative explanation is that only minimal hematoma occurred at the arteriotomy site in these patients.

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"Submaximal" Predischarge Exercise Testing After Acute Myocardial Infarction: Who Needs It?

ROBERT F. DeBUSK, MD, and CHARLES A. DENNIS, MD

Submaximal exercise electrocardiography performed before hospital discharge is safe and effective in stratifying prognosis and characterizing functional capacity in patients after acute myocardial infarction (AMI). However, there are reasons to question whether predischarge submaximal exercise electrocardiography represents optimal usage of this technique. Specifically, such testing appears to be inferior to symptom-limited testing 21 days after AMI for distinguishing high-risk from low-risk patients and for providing guidelines for the resumption of customary activities in the first month or two after AMI.

Patients have a substantially higher peak heart rate, blood pressure and workload response to symptom-limited testing at 3 weeks than during earlier testing.[1,4] Even when the peak heart rate at 3 weeks is similar to that achieved *at the same symptom limit* at 2 weeks, the peak workload of the later test exceeds that of the earlier one. This appears to reflect both physiologic and motivational factors. The former include a more complete reversal of bedrest-induced depletion of intravascular volume[5] and a lesser suppression of peak heart rate which results from AMI.[6] The latter include a lesser reluctance of the patient to exert to a true symptom limit as opposed to attainment of a "submaximal" heart rate and a lesser reluctance of the physician to exhort patients to a truly symptom-limited performance. These differences between submaximal and symptom-limited testing take on added significance as the average hospital stay for postinfarction patients decreases to 7 to 10 days or less.

The peak workload elicited by symptom-limited testing at 3 weeks has prognostic value independent of exercise-induced angina and ischemic ST-segment depression.[7,8] A low peak treadmill workload reflects a decrease in left ventricular ejection fraction and reversible ischemic thallium perfusion defects.[8] Both of these abnormalities have prognostic significance in postinfarction patients.[9,10]

We have found that symptom-limited exercise electrocardiography and radionuclide ventriculography performed at 3 weeks have equal prognostic value; symptom-limited exercise thallium myocardial perfusion scintigraphy added little to the combination of these two tests for predicting later cardiac events.[8] In contrast, Gibson et al[10] found that exercise thallium myocardial perfusion scintigraphy has greater prognostic value than exercise electrocardiography when a "submaximal" test protocol was used before hospital discharge. Similarly, Corbett et al[9] found that radionuclide ventriculography performed in conjunction with submaximal exercise has greater prognostic value than submaximal exercise electrocardiography. Leppo et al[11] found that dipyridamole-thallium-201 scintigraphy performed *at rest* 10 to 16 days after AMI is more sensitive than submaximal exercise electrocardiography in predicting future cardiac events.[11]

The distinction between high- and low-risk postinfarction patients can be accomplished with nearly equal predictive accuracy by a variety of methods: symptom-limited exercise electrocardiography or radionuclide ventriculography performed at 3 weeks, submaximal exercise thallium perfusion scintigraphy or radionuclide ventriculography performed before discharge and rest dipyridamole–thallium-201 scintigraphy performed before discharge. However, symptom-limited exercise electrocardiography is superior to all of the other methods for determining the ceiling of functional capacity on which to base recommendations for the resumption of customary physical activities, including occupational work.

Because the prognostic value of symptom-limited exercise electrocardiography performed at 3 weeks rivals that of radionuclide techniques for prognostic stratification[8] and is substantially cheaper, it is reasonable to ask, "Why the rush to perform predischarge exercise testing, with or without radionuclide imaging?"

Proponents of predischarge exercise testing argue that patients may have a reinfarction or die in the 10 to 14 days between hospital discharge and the 21st day. This has not been our experience with over 1,000 men aged 70 years or younger who were considered eligible for symptom-limited 3-week testing because they were free of complications by the 10th hospital day. Of these, 5 (0.5%) had either a reinfarction (3 cases) or died from cardiac causes (2 cases) between the 10th and 21st days after AMI. Offsetting this very small risk is the fact that treadmill-induced deaths after AMI, though infrequent,

From the Cardiology Division, Cardiac Rehabilitation Program, Stanford University School of Medicine, Palo Alto, California. Manuscript received October 9, 1984, accepted October 10, 1984.

Address for reprints: Robert F. DeBusk, MD, Director, Stanford Cardiac Rehabilitation Program, 730 Welch Road, Suite B, Palo Alto, California 94304.

tend to occur before the 14th day after the acute event. The safety argument for predischarge exercise testing thus appears to have little merit in clinically low risk patients who are free of congestive heart failure and unstable angina pectoris.

Another argument advanced for predischarge testing is that such testing is required to provide "clearance" for patients to resume customary activities at home during the 10- to 21-day interval. This argument is equally groundless in patients who are carefully evaluated before hospital discharge. A good prognosis, i.e., low risk of cardiac events from 10 to 14 and 21 days based on clinical characteristics is associated with a well-preserved functional capacity[3]: clinically low risk patients rarely have significant symptomatic limitation during this brief period.

In fact, the widespread policy of submaximal predischarge exercise testing reflects the historical development of the technique and the unique circumstances under which exercise testing is performed in tertiary care university centers, from which most clinical research reports emanate. Early postinfarction treadmill testing was a radical departure from standard clinical practice when the first studies were reported in the U.S.[12,13] Submaximal heart rate–limited protocols were believed safer, a major consideration in the early research.

Later studies adopted the submaximal protocols for these historical reasons and for logistical reasons common to academic medical centers; investigators in these institutions rarely know their AMI patients before admission and are unlikely to see them after hospital discharge. Because of the imperative to examine a "captive" population and the importance of maintaining continuity of a patient database, predischarge submaximal exercise testing has been perpetuated in academic investigations. However, the logistic difficulties encountered in research hospitals should not determine policies in primary care community hospitals where most patients with AMI are treated. Indeed, patients in community hospitals can and do return for testing at 3 weeks. In our experience, more than 95% of patients judged eligible for symptom-limited testing at 3 weeks actually appear for such testing. These patients are treated in community hospitals, primarily in Kaiser-Permanente hospitals within a 30-minute drive from the Stanford Medical Center.

A final reason for the common policy of predischarge exercise testing is the greater convenience it affords the physician. Although this is not a trivial consideration, especially for the physician, it must be weighed against more compelling considerations. For example, DRG reimbursement will exert pressure to defer exercise testing until after hospital discharge. There appears to be little risk in doing so in clinically low-risk patients. Predischarge testing could then be reserved for clinically "high-risk" patients, many of whom will undergo coronary arteriography in preference to exercise testing of *any* sort. Insurance coverage for "early" exercise testing is equally available for inpatient and outpatient testing performed 7 to 35 days after AMI.

These considerations are important in assuring that postinfarction patients receive an optimal evaluation. If logistic considerations preclude outpatient testing, predischarge testing is preferable to none at all. However, a sharp distinction should be drawn between logistic as opposed to medical imperatives for predischarge testing in clinically uncomplicated postinfarction patients.

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Billowing, Floppy, Prolapsed or Flail Mitral Valves?

JOHN B. BARLOW, MD, and WENDY A. POCOCK, MB FRCP

More than 2 decades ago the auscultatory features of a late systolic murmur and non-ejection systolic click were shown to originate at the mitral valve.[1] Left ventricular cineangiocardiography confirmed that late systolic murmurs were indicative of mild mitral regurgitation and demonstrated "massive dilatation," "aneurysmal protrusion," "billowing" or "ballooning" of the posterior mitral leaflet.[2,3] Later studies showed that the anterior leaflet was also involved. In 1966, Criley et al[4] clarified the cineangiocardiographic appearances and introduced the term prolapse. Mitral valve prolapse (MVP) is now a widely used term regardless of whether the valve anomaly is anatomically mild, echocardiographically demonstrable, functionally normal or clinically silent. This has contributed to the general confusion, and it is now crucial for the terms billowing, floppy, prolapse and flail to be defined. Such definitions should be based essentially on the functional anatomic, or pathologic, characteristics of the mitral valve mechanism. Auscultatory, echocardiographic, cineangiocardiographic and other clinical features should then be correlated with the probable functional anatomy. It is, after all, the functional anatomy of the mitral valve mechanism that we attempt to assess by all invasive or noninvasive investigations.

We recently expressed the view[5] that the concept propounded by the French cardiac surgeon, Alain Carpentier, defines the essential differences between prolapse and billowing. In this context Carpentier restricts the use of the term prolapse to failure of the leaflet edges to appose normally. Such partial loss of apposition may occur with or without abnormal billowing of the bellies of the leaflets, and mitral regurgitation, albeit mild or even minimal, will inevitably result. This concept of prolapse implies that the valve function is abnormal which is, in fact, both appropriate and correct. Any cardiac valve, provided there is not a hole or a cleft in a leaflet, remains competent while there is sustained coaptation of the leaflet edges. Prevention of apposition may occur if 1 or more leaflets are fibrosed or retracted. If leaflets are normal in size or larger, failure of sustained apposition will result in prolapse. Based on Carpentier's understanding of MVP, we consider that the following terms, which reflect normal and abnormal mitral valve functional anatomy, should clarify much of the current confusion.

The normal mitral leaflets billow slightly, after closure, into the left atrial cavity (Fig. 1A). Exaggeration of this (Fig. 1B), which may range in severity from being marked and diffuse to mild and involving only 1 scallop or even part of a scallop,[6] should be termed a billowing mitral leaflet (BML). This BML may produce a non-ejection click, but mild BML may not be evident on echocardiography or cineangiocardiography. Conversely, BML sufficiently prominent to be demonstrated by these methods of investigation, may not always be detected on auscultation. If the BML progresses, disruption of leaflet edge apposition may ensue and MVP is the result (Fig. 1C). Once there is MVP, mitral regurgitation is inevitable and is reflected clinically by a mitral systolic murmur. Because the BML is more marked it may be demonstrated on echocardiography, but echocardiography, whether M-mode or 2-dimensional, detects systolic displacement of the body of a leaflet and not disengagement of leaflet edge coaptation. If the BML is extreme with very voluminous leaflets and elongated chordae, the term floppy is appropriate. MVP is almost always present with a floppy valve (Fig. 1D) and the mitral regurgitation is often

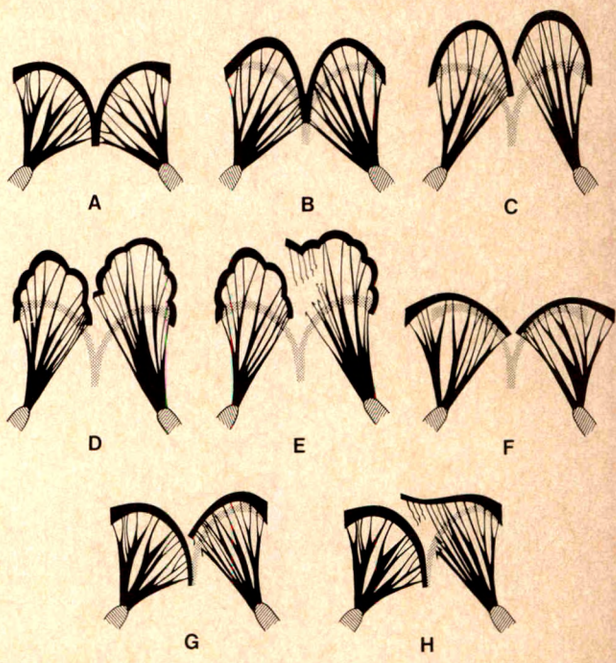

FIGURE 1. Billowing (BML), floppy, prolapsed (MVP) and flail mitral valves. **A,** normal mitral valve showing papillary muscles, chordae tendineae and apposed leaflet edges. **B,** BML; the chordae are lengthened and the voluminous leaflets "billow" into the left atrium. In this and subsequent drawings, the positions of normal leaflets are superimposed with a **stippled** pattern. **C,** BML with MVP; the valve is incompetent. **D,** floppy valve with MVP. **E,** floppy valve and flail leaflet. Marked regurgitation is present. **F,** recent onset anular dilatation causes MVP with minimal BML due to loss of "keystone" effect. **G,** a ruptured minor chorda allows MVP without detectable BML. **H,** flail leaflet with mild BML.

From the Cardiovascular Research Unit, Department of Cardiology, University of the Witwatersrand and the Johannesburg Hospital, Johannesburg, South Africa. Manuscript received September 17, 1984, accepted September 24, 1984.

Address for reprints: John B. Barlow, MD, Department of Cardiology, Johannesburg Hospital, Private Bag X39, Johannesburg, 2000 South Africa.

holosystolic. Echocardiography will readily confirm the floppy leaflets but not the MVP. Progression of the MVP with a floppy valve or with a BML may result in ruptured, or at least grossly elongated, chordae and part of the leaflet will then be flail (Fig. 1E). Mitral regurgitation is now hemodynamically significant and the displacement of the leaflet edge is readily apparent on echocardiography. Thus, although there is overlap and the dividing margins are somewhat ill-defined at present, floppy is the extreme of marked BML and flail that of severe MVP.

Expanding further on Carpentier's concept of "prolapse," MVP may occur with insignificant BML. This could result, for example, from rupture of a minor chord (Fig. 1G) as a result of infective endocarditis on a normal or near-normal mitral valve. Progression to flail, still without BML, could occur after rupture of a major chorda tendinea or with multiple chordal rupture (Fig. 1H). Functionally lengthened chordae due to papillary muscle dysfunction could also cause MVP, sometimes temporarily, without detectable BML. Another mechanism for MVP with only mild BML is recent onset anular dilatation (Fig. 1F). When the "keystone effect"[7] of leaflet edge apposition is diminished, the chordae are subjected to greater tension, and MVP may supervene. In our experience, a principal cause of recent-onset anular dilatation without BML is acute rheumatic carditis. More widely recognized is the combination of a dilated anulus with either marked BML or floppy valve. Anular dilatation, voluminous leaflets and elongated chordae are the characteristic morphologic features[8] of the "floppy valve syndrome,"[9] with or without skeletal manifestations of the Marfan syndrome.

A BML may be a result of a degenerative process[10] (primary BML) or be secondary[11] to other valvular or myocardial pathology (secondary BML). Irrespective of whether protrusion of leaflet scallops into the left atrium can be shown on echocardiography, a BML on its own is a functionally normal valve as far as not allowing incompetence is concerned. Primary BML, whether identified by "echo only"[12] or by hearing an isolated nonejection click,[11] may thus be regarded as a "variant of normal," especially in asymptomatic subjects. When symptoms, electrocardiographic changes, arrhythmias or other features occur, the recognition of a syndrome is justified and for many years we have preferred "billowing mitral leaflet syndrome" to denote that common condition. When a BML is relatively more severe, leaflet edges fail to remain in apposition, mitral regurgitation supervenes and this is MVP. We emphasize that MVP should be detected on auscultation but that mitral regurgitation can only be confirmed, if this is believed necessary, on cineangiocardiography or possibly by Doppler ultrasound. Furthermore, whereas echocardiography may demonstrate the BML, it does not show the MVP until it is very severe or a leaflet flail.

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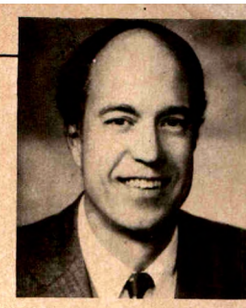
Enticing Real and Potential Cardiovascular Researchers Away from Research



The number of physicians increases each year. Every city in America probably has too many physicians. For the first time in decades, several medical schools in 1984 decreased the number of students admitted to the freshman medical school class.

It appears that there are now too many cardiologists—both adult and pediatric—and cardiovascular surgeons in the USA. Certainly there are too many in the major cities. Competition is getting stiff, but nevertheless the financial reward continues to be good, particularly for those doing invasive procedures. I understand that the cardiologist's fee for coronary angioplasty is usually about $2,500, but that it can be twice that amount. A number of surgeons have told me that their fee for coronary artery bypass surgery usually is about $5,000, with sometimes $2,000 more for the surgical assistant; of course, the anesthesiologist's fee is separate. A cardiac-surgeon friend told me 5 years ago (February 1980) that a cardiac surgeon not making "half a million dollars a year was simply not a good cardiac surgeon." A half million, of course, is derived from 100 bypass operations or an average of only 2 a week. A few valve replacement operations additionally each year take care of the office expenses and malpractice insurance. Although most cardiac surgeons do coronary bypass operations and, therefore, most in private practice receive these high incomes, most cardiologists (however that might be defined[1]) do not do invasive procedures, and furthermore most who do invasive procedures do not do angioplasty. But the noninvasive procedures are also large financial generators in cardiology. Compared with other subspecialties of internal medicine, the income of adult cardiologists is usually substantial. The division of cardiology is the largest generator of income of any subdivision of internal medicine. Thus, both cardiology and cardiovascular surgery are financially rewarding, the most rewarding in these terms of any subspeciality of surgery or any subspeciality of medicine or pediatrics.

Is this high financial reward today in cardiologic practice (either medicine, pediatrics or surgery) too enticing to the creative mind which a decade or so ago would have relished a career in cardiovascular research? I think the answer is yes. Of course, there may be other factors. The young potential investigators observe the difficulty of their senior faculty in obtaining and retaining research grants. They observe the frustration of the senior faculty in trying to do research while managing large clinical responsibilities to generate their incomes. They observe the difficulty of their superiors in getting their research papers published, the near "harrassment" from reviewers and editors, neither of whom "really understand their papers." They observe in surprise the actual energy—both physical and mental—required to create and to generate the data to prove or disprove the idea and the discipline it takes to "package" the product once the results of the investigation are clear.

Although available clinical positions in cardiovascular medicine and surgery are decreasing, positions for cardiovascular researchers are plentiful and good candidates are few[2]. Despite the relative decrease in federal monies for cardiovascular research, pharmaceutical and other private monies are increasing. Money is and will be available to support the good ideas and the good research, but more resourcefulness is now required of the investigator. Cardiovascular disease will not be conquered by doing more coronary angioplasties or bypasses or performing more echocardiograms or nuclear angiograms. But successful research is a selfish and demanding mistress. She never lets up. She disdains fancy cars, elaborate boats, long vacations, too many long weekends, season tickets for this or that, and so on. But, opportunity to utilize one's potential to the fullest is sufficient reward.

William C. Roberts

William C. Roberts, MD
Editor-in-Chief

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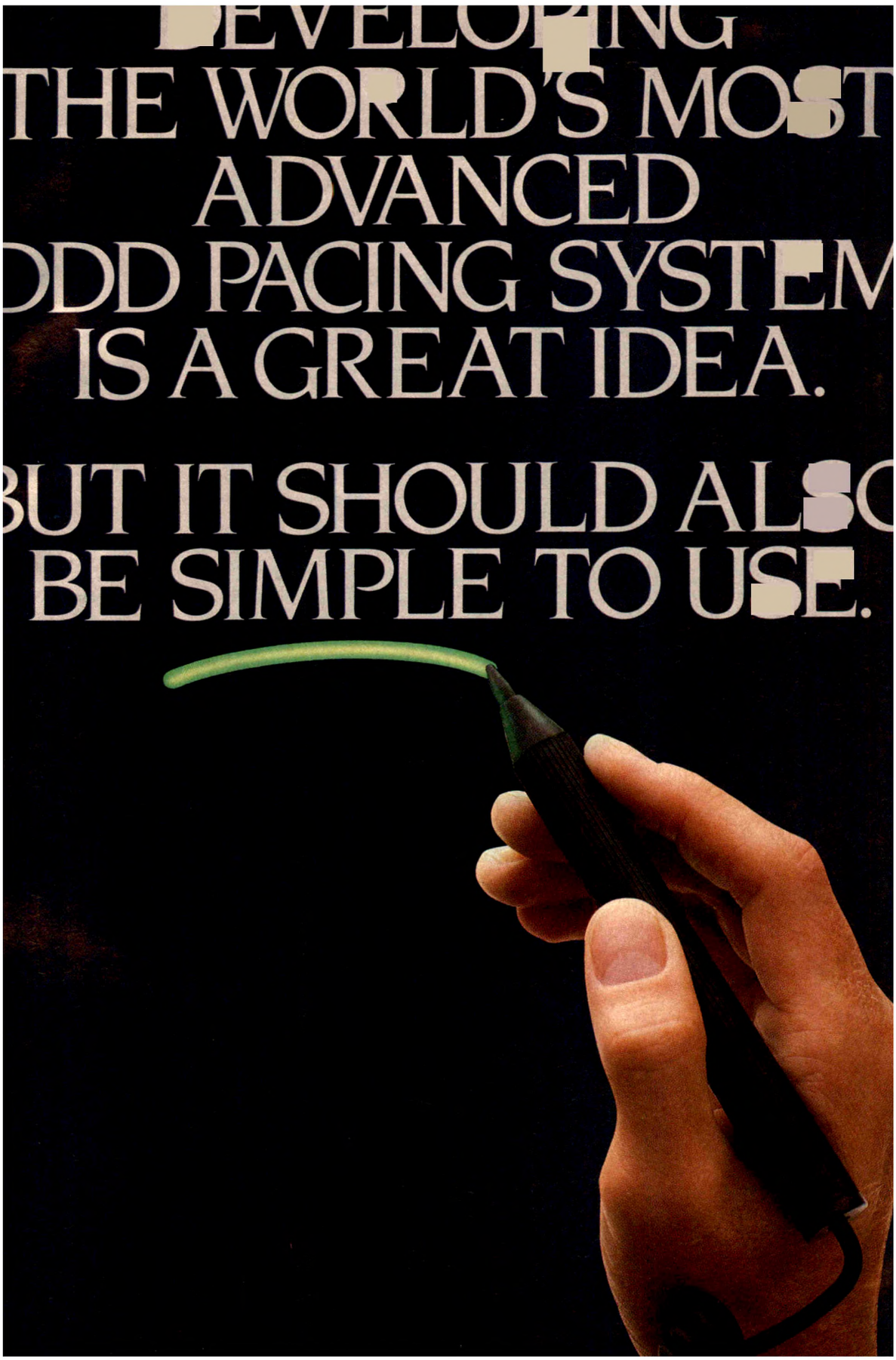

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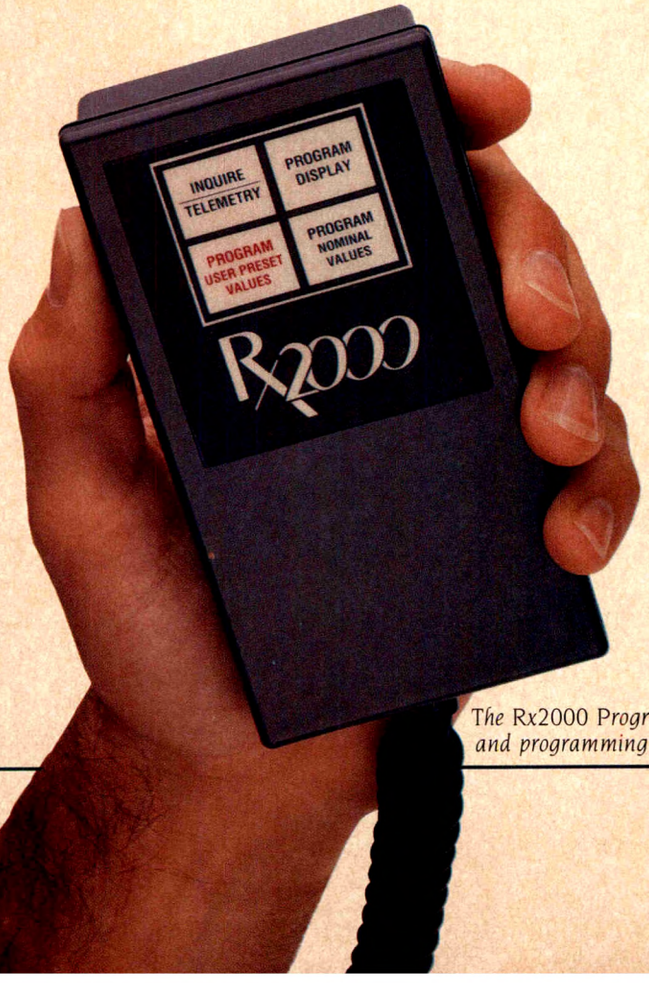

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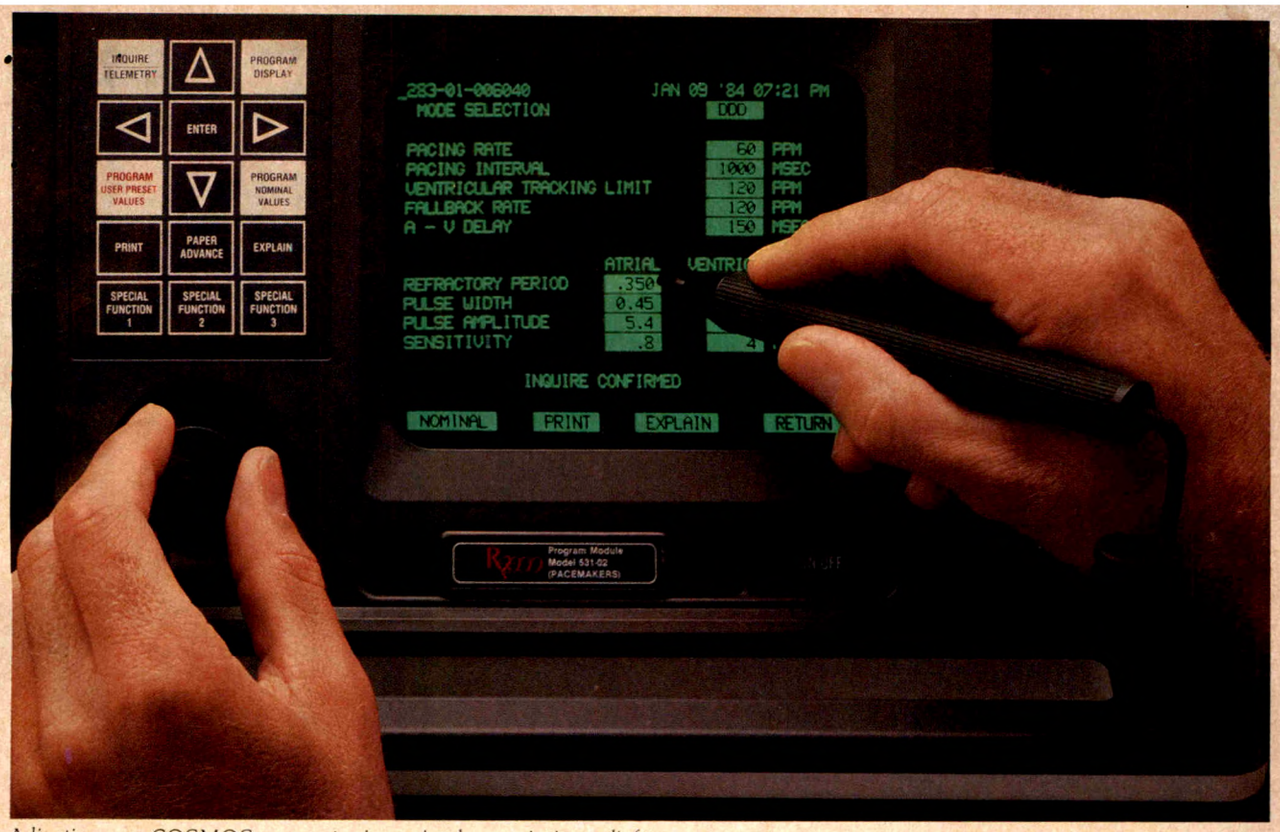

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Contraindications: For patients exhibiting atrial fibrillation or atrial flutter, careful individual consideration should precede the use of the VDD or DDD mode, since rapid ventricular tracking could ensue.
In cases of chronic atrial fibrillation or atrial flutter, the use of any dual chamber pacing mode may be clinically ineffective.
In patients exhibiting slow retrograde (V-A) conduction, use of the VDD or DDD mode could give rise to pacemaker-mediated tachycardias.

Possible complications: Complications associated with pacemaker implantation include pacemaker-induced arrhythmias; infection; skin erosion; pulse generator migration; hematoma; fluid accumulation; and histotoxic reactions.

Precautions: For the effects of electrical or magnetic interference, defibrillation, diathermy, therapeutic radiation, and industrial or other special environments, see the Physician's Manual accompanying the pulse generator.

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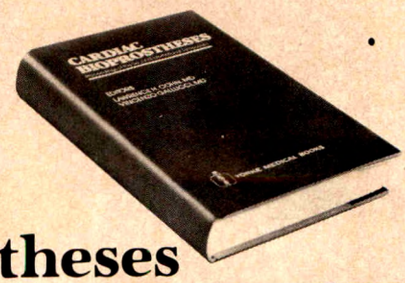

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $69.00

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

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If your interests include the clinical, pathological and bioengineering aspects of cardiac bioprostheses then this book is a *must buy!* It should not be missing from your own professional library.

Who are the editors?

Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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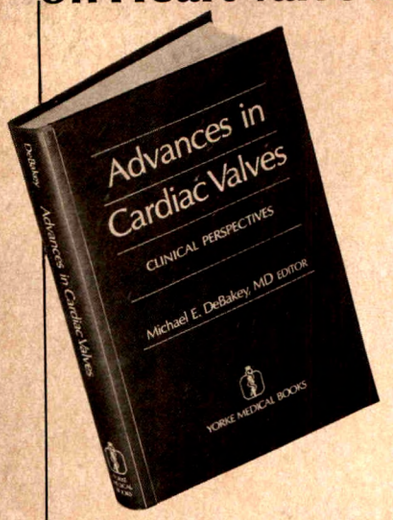

Advances in Cardiac Valves
Clinical Perspectives

edited by **Michael E. DeBakey, MD**

0-914316-40-0, November 1983, 274pp., $35.00

This valuable new clinical reference provides a detailed update on many aspects of mechanical heart valve prostheses, including hemodynamics, clinical results, results in children, non-invasive assessments, special indications, and implant techniques. Each topic is presented in an easily understood style and format which facilitate the comprehension of recent developments in heart valve replacement for the busy clinician.

Each chapter is written by internationally respected physicians and medical scientists each of whom is pre-eminent in his field. All of this information has been co-ordinated by Dr. DeBakey to produce a very readable and informative volume on the state-of-the-art of heart valve replacement with mechanical prostheses. No cardiologist, cardiovascular surgeon, internist, or bioengineer can afford *not* to be knowledgeable about the information in this book.

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CONTRIBUTORS INCLUDE

Mauro Abbate
Franz W. Amann
Manuel J. Antunes
Kit V. Arom
P. Barzellotti
Enrico Baruffi
Giuseppe Battaglia
Eugene M. Baudet
Marco Benedetti
Dieter Burckhardt
Jorge L. Camunas
R. Carlier
E. Stanley Crawford
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Michael E. DeBakey
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Reference: 1. National survey of 2960 physicians, including 1502 cardiologists and other physicians subspecializing in cardiology, conducted by Hoechst-Roussel Pharmaceuticals Incorporated, Somerville, New Jersey. August 1982.

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WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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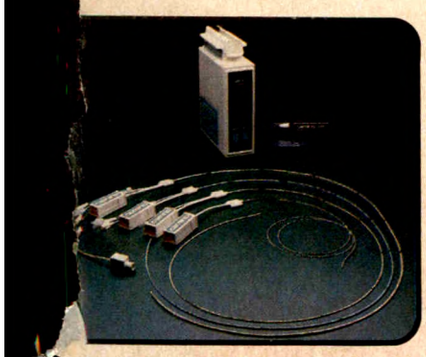

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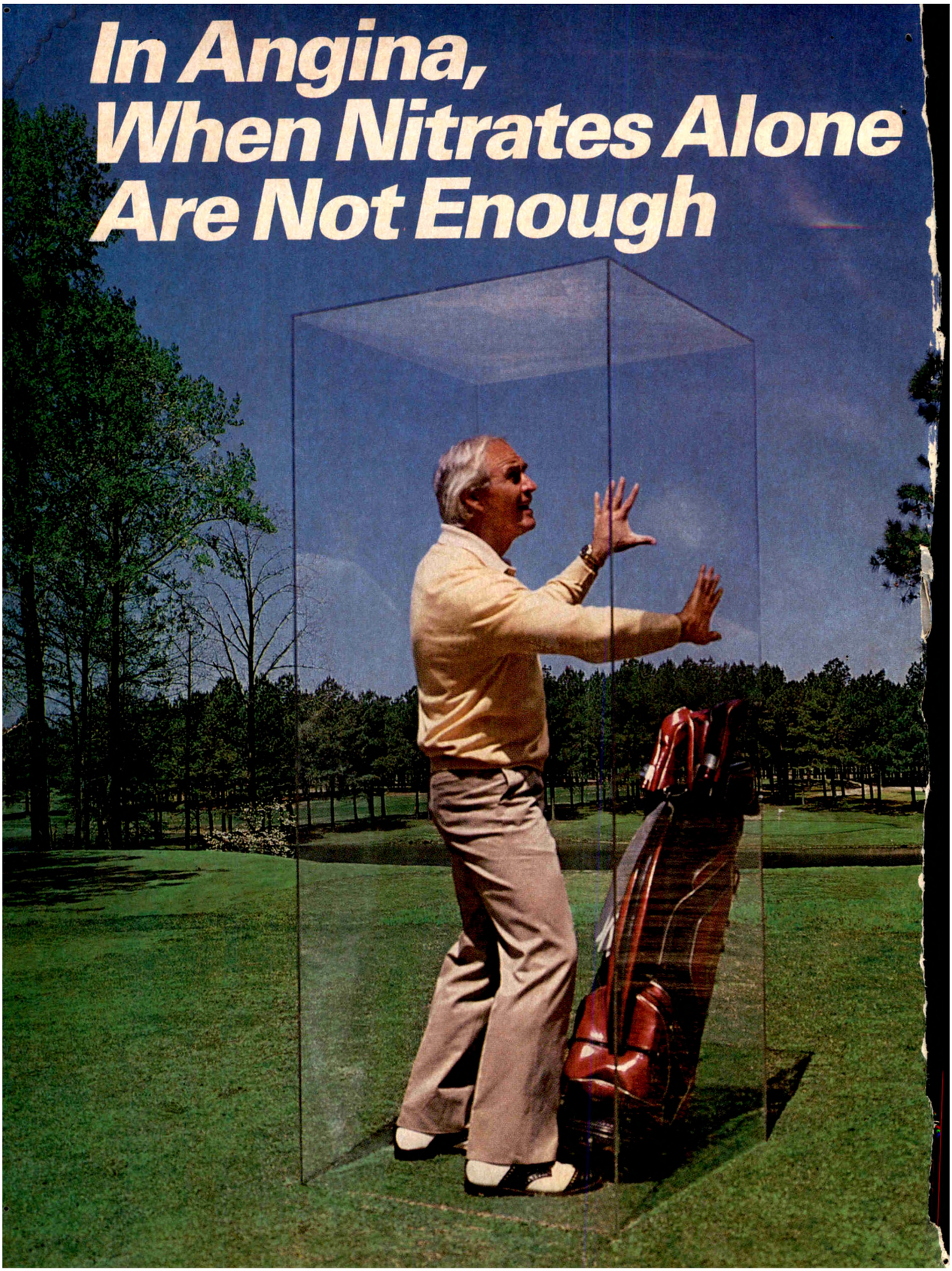
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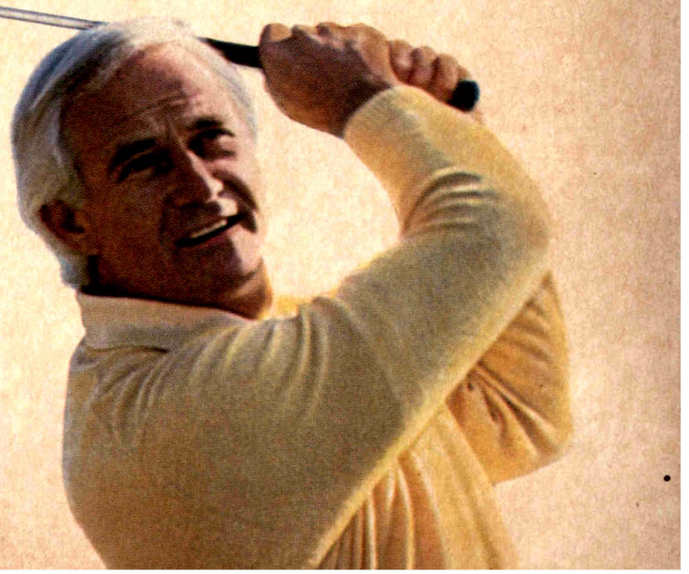

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block.

Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension, usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Elevations of liver enzymes have been reported. Four cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in less than 0.5% of patients, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions, spotty menstruation, ecchymosis, bruising, gynecomastia, and psychotic symptoms. Overall continuation rate was 94.5% in 1,166 patients.

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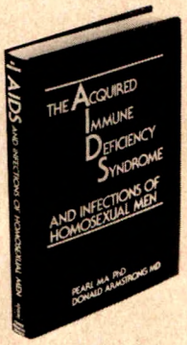

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Acquire Immune Deficiency Syndrome (AIDS) and Infections of Homosexual Men

edited by **Pearl Ma, PhD,** and **Donald Armstrong, MD** with a foreword by **David J. Sencer, MD,** *Commissioner of Health, New York City; formerly Director, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services*
0-914316-38-9, 442 pages, illus., 1984, $39.50

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AIDS has become one of the most publicized diseases in modern times. It has produced fear and confusion in the general public and presented a formidable challenge to the medical community. Physicians and scientists have begun work on managing this epidemic, disease control centers continue to search for answers, and the federal government has declared AIDS the number one health priority of the nation. Understanding this disease demands cooperation between many different medical specialties, and papers on this subject have been published in many diverse journals not regularly read by individual specialists. Now, for the first time, two highly distinguished medical experts, Drs. Pearl Ma and Donald Armstrong, have coordinated in one easily accessible volume the complete range of interdisciplinary approaches to this complex disease, with contributions by the most eminent researchers and physicians in disease control and hospital teaching centers throughout the country. Comprehensive coverage is given to the entire spectrum of sexually transmitted diseases, and an additional section on diagnostic perspectives offers never before published material on why this syndrome occurs primarily among homosexual men. For any physician or other health care professional interested in the prevention and cure of this modern epidemic, this book is an indispensable guide to recognizing and treating AIDS and other sexually transmitted diseases.

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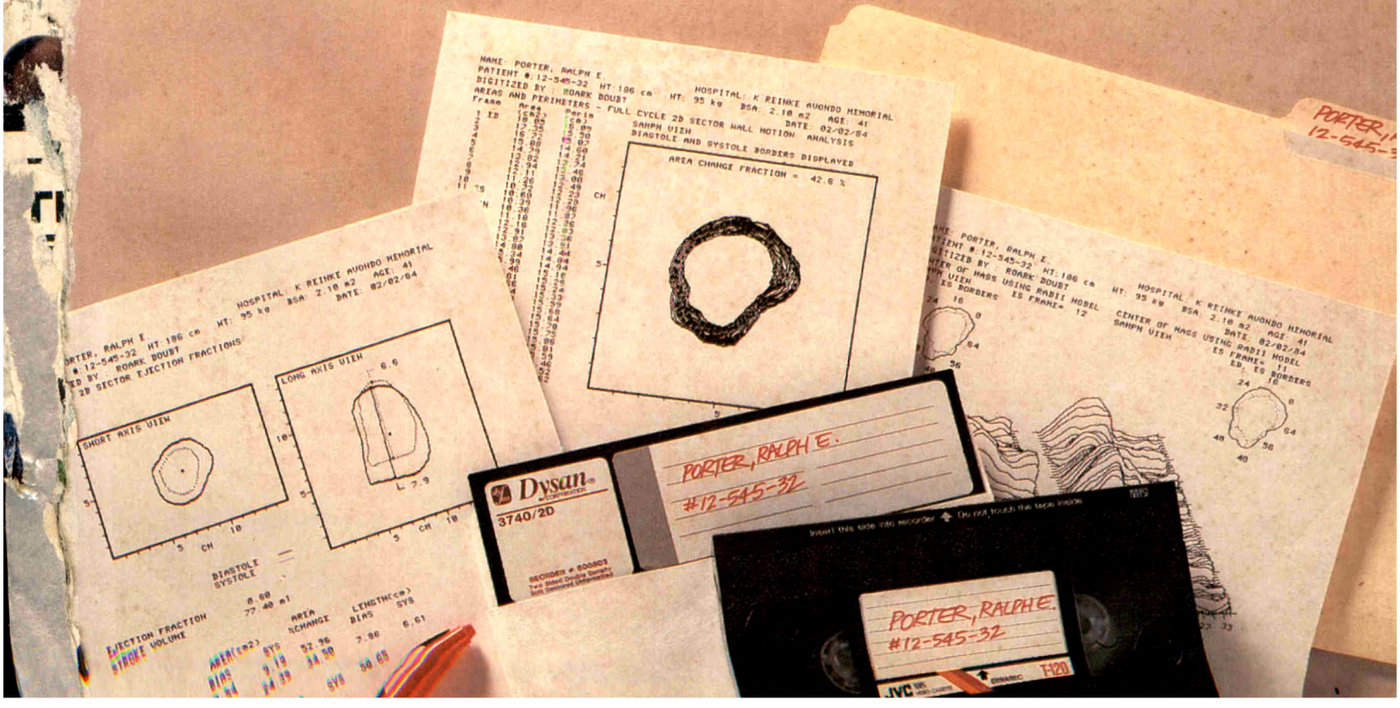

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For steady maintenance following cardioversion of supraventricular, ventricular, and atrial tachyarrhythmias

- Maintains normal sinus rhythm
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- Greater gastrointestinal tolerance than with quinidine sulfate*
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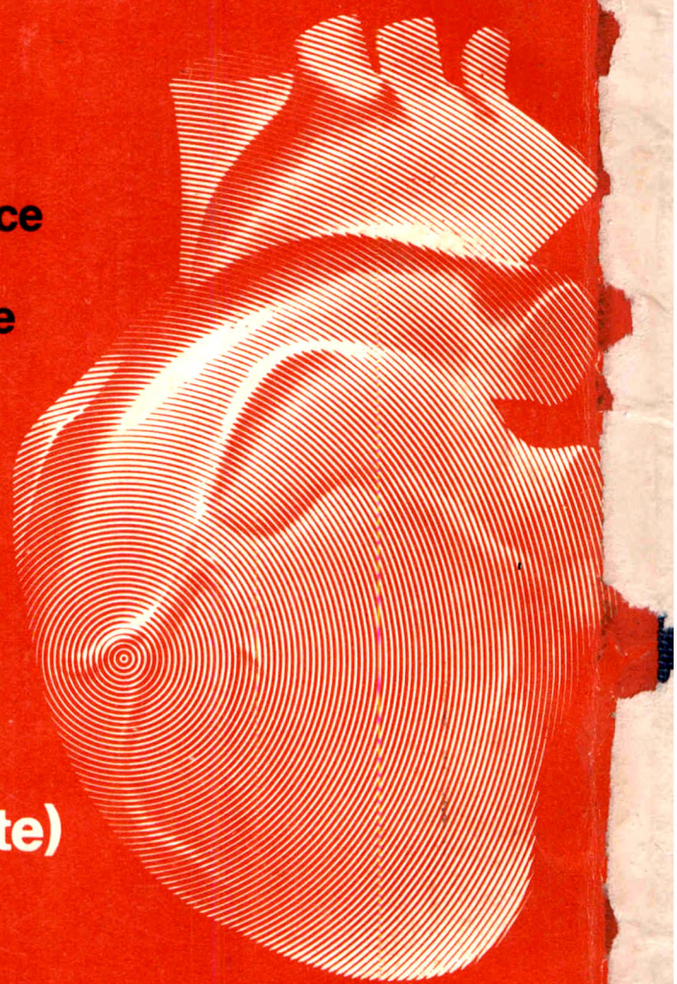

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

INDICATIONS AND USAGE: CARDIOQUIN Tablets are indicated as maintenance therapy after spontaneous and electrical conversion of atrial tachycardia, flutter or fibrillation and in the treatment of premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, and paroxysmal ventricular tachycardia when not associated with complete heartblock. CONTRAINDICATIONS: History of hypersensitivity to quinidine, complete A-V block, complete bundle branch block or other severe intraventricular conduction defects, myasthenia gravis, arrhythmias associated with digitalis toxicity. WARNINGS: In the treatment of atrial fibrillation with rapid ventricular response, use digitalis to control ventricular rate prior to administration of quinidine. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine. *Potentially toxic digoxin plasma levels may occur when quinidine is administered concurrently. Consider reducing digoxin dosage and monitoring for digitalis toxicity.* Evidence of quinidine cardiotoxicity (increased P-R and Q-T intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia) mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. NOTE: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia. Quinidine should be used with extreme caution in the presence of incomplete A-V block, since complete block and asystole may result. Quinidine may cause abnormalities of rhythm in digitalized patients; therefore, it should be used with caution in the presence of digitalis intoxication. Caution is also called for in patients exhibiting renal, cardiac or hepatic insufficiency because of potential toxic accumulation of quinidine in plasma. PRECAUTIONS: A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncracy to quinidine. ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered. Periodic blood counts and liver and kidney function tests should be performed during long-term therapy.

DRUG INTERACTIONS OF QUINIDINE:

DRUG	EFFECT
With anticholinergic drugs	Additive vagolytic effect.
With cholinergic drugs	Antagonism of cholinergic effects.
With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decrease excretion of quinidine.
With coumarin anticoagulants	Reduction of clotting factor concentrations
With tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
With phenothiazines and reserpine	Additive cardiac depressive effects.
With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine.
With digoxin	Increased plasma concentrations of digoxin (see WARNINGS).

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: The drug should be used with caution due to excretion of the quinidine in breast milk. ADVERSE REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/or disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTESTINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricular tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMATOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision, disturbed color perception, [illegible] blurred vision, disturbed color perception, [illegible] blindness, scotomata), [illegible]

Purdue Frederick

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